UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

BIOTECHNOLOGY INNOVATION ORGANIZATION; CALIFORNIA LIFE SCIENCES ASSOCIATION; and BIOCOM CALIFORNIA,

Plaintiffs,
v.

ALEX M. AZAR, II, in his official capacity as SECRETARY OF THE UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; SEEMA VERMA, in her official capacity as ADMINISTRATOR OF THE CENTERS FOR MEDICARE AND MEDICAID SERVICES; and THE CENTERS FOR MEDICARE AND MEDICAID SERVICES,

Defendants.

Civil Case No: 20-cv-08603

DECLARATION OF CRAIG GARTHWAITE, PHD

December 11, 2020

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I, Craig Garthwaite, declare as follows.

I. INTRODUCTION

A. Case overview

1. On May 11, 2018, President Trump released his "Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs." According to the Centers for Medicare & Medicaid Services ("CMS"), the Blueprint outlined steps the "administration is taking to combat high drug prices, end foreign freeloading, and spur biomedical innovation."[1]

2. In October 2018, CMS released an advance notice of proposed rulemaking (ANPRM) (83 FR 54546) ("ANPRM" or "October 2018 ANPRM").[2] The ANPRM proposed a number of new regulations for Medicare Part B, including:

- International Pricing Index ("IPI"): The Medicare payment amount for selected Part B drugs is based on the average prices paid for these drugs in selected countries[3] and a fixed add-on payment amount per dose.[4]
- Vendor Model: Replace the current "buy and bill" model in which providers buy drugs from wholesalers, purchasing organizations, or manufacturers and then bill Medicare Part B for these drugs, with a vendor model in which private-sector vendors negotiate prices for drugs, take ownership of them, and compete for providers, thus reducing providers' risk associated with furnishing the included drugs.
- Test and Control Geographies: Providers in randomly selected geographies, accounting for approximately 50 percent of Medicare Part B spending on separately

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[1] Centers for Medicare & Medicaid Services, 42 CFR Part 513, RIN 0938-AT91, Most Favored Nation (MFN) Model, November 20, 2020 ("CMS-5528-IFC"), at 9.

[2] CMS-5528-IFC, at 9.

[3] The included countries are Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, and the United Kingdom. The ANPRM considered these countries "as they are either economies comparable to the United States or they are included in Germany's market basket for reference pricing for their drug prices, and existing data sources contain pricing information for these countries." International Pricing Index Model for Medicare Part B Drugs; Medicare Program, 83 Fed. Reg (210) 54246 (Oct 30, 2018), available at: https://www.govinfo.gov/content/pkg/FR-2018-10-30/pdf/201823688.pdf ("ANPRM"), p. 54557.

[4] ANPRM, p. 54547.

payable Part B drugs, would participate in the model, allowing for a comparison to a control group of geographies that do not participate. This would allow CMS to examine the effect of the IPI on a variety of important outcomes such as patient access, provider profits, manufacturer incentives to invest in R&D, and health outcomes.

3. The CMS, however, did not subsequently release a Notice of Proposed Rulemaking ("NPRM") related to the proposals above.

4. On September 13, 2020, the Trump Administration issued the "Executive Order on Lowering Drug Prices by Putting America First."[5] The Executive Order noted, among other things, that "the Medicare program should not pay more for costly Part B or Part D prescription drugs or biological products than the most-favored-nation price,"[6] and instructed the Secretary of Health and Human Services to

> immediately take appropriate steps to implement his rulemaking plan to **test a payment model** pursuant to which Medicare would pay, for certain high-cost prescription drugs and biological products covered by Medicare Part B, no more than the most-favored-nation price. The model would **test** whether, for patients who require pharmaceutical treatment, paying no more than the most-favored-nation price would mitigate poor clinical outcomes and increased expenditures associated with high drug costs.[7]

5. On November 20, 2020, in response to the September 13, 2020 Executive Order, the CMS issued the Interim Final Rule with Comment Period ("IFC") for Medicare Part B drugs and biologics.[8] The IFC set forth a number of new regulations for Medicare Part B that are set to be effective on January 1, 2021, six weeks after the IFC was issued. The following characteristics of the IFC stand out in contrast to the ANPRM:

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5 The White House, Executive Order on Lowering Drug Prices by Putting America First, September 13, 2020 ("Executive Order").

6 Executive Order, Section 2.

7 Executive Order, Section 3 (emphasis added).

8 CMS Fact Sheet, "Most Favored Nation Model for Medicare Part B Drugs and Biologicals Interim Final Rule with Comment Period", November 20, 2020 (https://www.cms.gov/newsroom/fact-sheets/fact-sheet-most-favored-nation-model-medicare-part-b-drugs-and-biologicals-interim-final-rule).

- Most Favored Nation ("MFN") Prices: The Medicare payment amount for selected Part B drugs is based on "the **lowest** per capita Gross Domestic Product-adjusted (GDP-adjusted) price of any non-U.S. member country of the Organisation for Economic Co-operation and Development (OECD) with a GDP per capita that is at least sixty percent of the U.S. GDP per capita,"[9] and a fixed add-on payment amount per dose.[10]

- "Buy and Bill" Model: The current "buy and bill" model, in which providers order, buy, receive, store, and administer drugs for Part B patients, remains in place, exposing providers directly to the burden and financial risk associated with furnishing the included drugs.[11]

- Nationwide and Mandatory Implementation: The MFN model includes all providers and suppliers, with limited exceptions, in all geographies in the U.S., who participate in the Medicare program.[12]

6. On December 4, 2020, in response to the IFC, plaintiffs[13] brought suit against the Secretary of the United States Department of Health and Human Services ("HHS"), HHS, the Administrator of the Centers for Medicare and Medicaid Services ("CMS"), and CMS.[14]

7. Plaintiffs allegations include

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9 CMS-5528-IFC, at 7.

10 CMS-5528-IFC, at 108-109.

11 CMS-5528-IFC, at 6-7.

12 CMS-5528-IFC, at 6.

13 Plaintiffs are Biotechnology Innovation Organization ("BIO"), on behalf of itself and its members, California Life Sciences Association, on behalf of itself and its members, and Biocom California, on behalf of itself and its members.

14 Complaint for Declaration of Injunctive Relief, Biogen Innovation Organization; California Life Sciences Association; and Biocom California v. Alex M. Azar, II, in his official capacity as Secretary Of The United States Department Of Health And Human Services; United States Department Of Health And Human Services; Seema Verma, in her official capacity as Administrator Of The Centers For Medicare And Medicaid Services; And The Centers For Medicare And Medicaid Services, December 4, 2020, at 1 ("Complaint").

- the IFC violates the "notice-and-comment requirements of the Administrative Procedure Act;"[15]
- HHS is impermissibly using its "limited authority to 'test' new payment 'models' as a basis for completely rewriting the reimbursement formula Congress enacted;"[16]
- the MFN Rule will "have significantly adverse impacts on patients and providers"[17] and an "adverse impact" on Plaintiffs' members;[18]
- HHS did not have "good cause […] to make the MFN rule immediately effective;"[19] and
- the MFN rule will "severely limit drug innovation and patient access."[20]

8. Plaintiffs requests include

- "a declaration that the MFN Rule is procedurally invalid;"
- a "preliminary and permanent injunction prohibiting defendants from implementing or enforcing the MFN Rule;"
- an "[a]ward of plaintiff's attorney fees and costs;" and
- other relief the Court "may deem just and proper."[21]

B. Assignment

9. I have been asked by counsel for BIO to provide my expert economic opinions to date on a number of aspects of the IFC. Specifically, I was asked to provide my preliminary assessments regarding whether

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15 Complaint, ¶ 1.

16 Complaint, ¶ 1.

17 Complaint, ¶ 84.

18 Complaint, ¶ 110.

19 Complaint, ¶ 103.

20 Complaint, ¶ 123.

21 Complaint, ¶167.

- the new regulations in the IFC are economically different than those proposed in the October 2018 ANPRM;
- the implementation of the MFN model described in the IFC is a proper test to assess the impacts of the model;
- the implementation of the IFC on January 1, 2021 would cause harm, including immediate and irreparable harm, to Medicare beneficiaries and other parties; and
- the implementation of the IFC on January 1, 2021, without following normal rulemaking requirements regarding notice and comment periods, is justified by new and unique economic impacts associated with the COVID-19 pandemic.

10. In conducting my assignment, I have relied on my own research and experience, relevant economic literature, and publicly-available information. A list of the materials that I have relied upon is provided in Appendix C. I also directed a team of employees from Analysis Group, Inc. ("Analysis Group"), an economics research and consulting group. I am being compensated at an hourly rate of $750. No compensation to me or to Analysis Group is contingent on my findings or on the outcome of this litigation.

11. This declaration summarizes the opinions that I have formed over a period of three weeks since the IFC was issued on November 20, 2020. My opinions are based on the research and analyses that I was able to undertake during this period and the information available to me as of the date of this declaration. My work in this matter is ongoing and I may amend or supplement my opinions and declaration, if necessary and appropriate, based on further review of information, research, and analyses.

C. Summary of conclusions

12. My preliminary analysis to date of the proposed regulation in the IFC leads me to conclude the following.

13. The economics of the new regulation in the IFC are materially different than those proposed in the October 2018 ANPRM. Notably, while the ANPRM proposed to test a new reimbursement model in *select geographic areas*, the IFC requires mandatory, *nationwide* participation of Medicare participating providers and suppliers (with limited exceptions). Furthermore, while the ANPRM proposed to test a reimbursement model that would set

Medicare Part B reimbursements based on the *average* GDP-adjusted price of a select group of countries, the IFC would set Medicare Part B reimbursements based on the *minimum* GDP-adjusted price of a *different set of countries*. The IFC also does not have a provision that was in the ANPRM for creating a set of private-sector vendors to purchase and take title to the drugs affected by the regulation. Instead, physicians will continue to purchase these drugs and bear the financial risk that Medicare reimbursements will be below the acquisition price. In contrast, the ANPRM sought to reduce the medical providers' burden and financial risks by having vendors negotiate prices, take title to the drugs, and compete for physician and hospital business.

14. The MFN model described in the IFC is not a properly-implemented setting to test the effects of this policy. The regulation is set to be implemented nationwide and requires mandatory participation by all Medicare Part B patients and providers (with limited exceptions). Therefore, a proper comparison of outcomes in the tested group of providers and patients to an untested control group is not feasible and it will not be possible to reliably and rigorously evaluate the consequences of the MFN model. When the scale of a proposed regulation is large and its consequences are uncertain, it is of particular importance that the demonstration model is a properly-implemented test in which the regulation's consequences can be evaluated, potential harm from the regulation during the testing period is limited, and the regulation can be improved over time before broad adoption. The MFN model described in the IFC is not set to be implemented in this way. The regulation also differs from tests that the Center for Medicare and Medicaid Services Innovation ("CMMI") has run in the past, which were limited in scope (e.g., pilots).

15. The implementation of the regulations only six weeks after the IFC was issued will create distinct harms to providers, patients, and manufacturers. Some of these harms will emerge immediately and are directly a consequence of the speed with which this regulation is implemented. Some of these immediate harms will be irreparable and persist long after this litigation. Others will manifest over time and some are likely unintended consequences of the regulation that would have been addressed during a more carefully considered policymaking process.

16. The IFC will cause immediate harm to medical providers, because the regulation, as written, does not directly constrain the prices manufacturers charge for their drugs. Instead, it limits the amount Medicare will reimburse providers for drugs that medical providers have already purchased or will purchase in the future. The sudden change in reimbursements will immediately harm providers because they have either already bought existing inventories of these products and/or have entered into long term purchase arrangements with pre-specified prices. The IFC acknowledges that providers may not be able to immediately (or ever) obtain lower prices from drug manufacturers to treat Medicare patients. Therefore, faced with the prospect of small or negative returns from treating Medicare patients with these drugs, where possible providers may avoid relatively unprofitable treatments for Medicare patients. For their existing inventory, to the extent that physicians are unable to shift to higher reimbursing patients, the rapid implementation of the IFC will cause an immediate harm. In addition, the IFC would change physicians' add-on payment for administering drugs under Part B from a percentage basis to a flat fee, a change that CMS has found will decrease average add-on revenues for 9 out of 35 medical specialties, including hematology/oncology, one of the top three billing specialties for 38 out of the 50 drugs included in year one of the MFN model. Furthermore, the sudden implementation of lower reimbursements and switching to a flat fee per dose with only a six week notice will impose undue administrative burdens and costs on medical providers to navigate and adapt to the new regulation.

17. The harms caused by the IFC would be particularly acute, immediate, and irreparable for U.S. patients that stand to lose access to their medications. The IFC acknowledges that reducing Medicare Part B reimbursements to providers will immediately reduce Medicare enrollees' access to their current medications. According to the IFC, the implementation of the MFN model is projected to decrease CMS' Medicare spending by nine percent in 2021 because certain Medicare enrollees would have "no access" to drugs that they previously would have been able to access. The harm to patients from reduced access to drugs will be immediate and irreparable, because the lack of access to certain drugs, or switching to an inferior treatment, cannot be reversed later. Once a patient forgoes, delays, or changes treatment, they cannot go back in time to change that decision.

18. The projected reduction in access to *existing* drugs is only part of the irreparable harm to U.S. patients. Investing in biotech research and development ("R&D") is both risky (most biotech projects fail) and costly (typically requiring investments of billions of dollars to bring a product to market). As a result, by reducing the potential financial upside of developing new products, the IFC will reduce investments in biotech R&D, which, in turn, will slow down biotech innovation and lead to a reduction in the development of new products. Importantly, this lack of new products represents its own form of reduced access and irreparable harm to patients in the future, because those patients would be permanently deprived of drugs that do not get developed and patients would be denied timely access to drugs for which the development or approval for a new indication is delayed due to the immediate implementation of the IFC.

19. The sudden implementation of the IFC would also be expected to cause an immediate decline in revenues and profits for manufacturers. This unexpected loss in revenues and profits will come from, at least, two channels. First, drug manufacturers may respond to the non-market-based lowering of Medicare reimbursements by lowering the prices that they charge, which will decrease their revenues and profits. Second, if drug manufacturers do not sufficiently lower the prices that they charge, their sales will decrease, because some providers will not be willing to administer the product to Medicare patients. Third, drug manufacturers may respond to the IFC by charging inefficiently high prices internationally, which will decrease their sales and profits. Furthermore, the IFC would, as described above, reduce investments in biotech R&D by reducing the maximum and/or expected returns from developing a new treatment. The reduction in returns can decrease the ability of biotech firms, particularly small biotech startups, to secure funding for their business. A disruption in funding can be particularly harmful to small biotech startups that rely on outside capital to finance their operations. Furthermore, if unilateral action by a government agency that lowers prices / reimbursements immediately and substantially, without going through the normal rulemaking process, is allowed to go into effect, this would further add to the uncertainties to the prospects of future investments in the biotech industry and chill investment. The harm would be immediate and irreparable to biotech firms that cannot secure timely funding to start or continue their R&D. Even if the firms can secure funding at a later time, they cannot recover the research time lost, and, in some

cases, the R&D may no longer be profitable to pursue due to, for example, pending patent expirations.

20. Implementing the IFC immediately in response to the economic impacts of the COVID-19 pandemic is not justified. While CMS claims that the IFC will "prevent stinting on care" that may otherwise occur in response to financial hardships due to the pandemic, the IFC actually threatens to *cause* "stinting on care" by reducing Medicare enrollees' access to drugs. Furthermore, while CMS claims that the IFC needs to be implemented immediately in response to high unemployment and financial hardships, most Medicare enrollees are older Americans that are not in the labor force (and therefore, not unemployed due to the COVID-19 pandemic) and most have supplemental insurance that covers at least part of their out-of-pocket costs. To the extent that CMS aims to alleviate the financial hardships of Medicare enrollees, there are other ways to provide direct economic relief. For example, CMS could reduce Medicare premiums or deductibles, but belying its purported concern for financial hardships during the pandemic, in November 2020, CMS announced an *increase* in Medicare premiums and deductibles for 2021.

D. Qualifications

21. I am the Herman R. Smith Research Professor in Hospital and Health Services and a tenured Professor of Strategy at the Kellogg School of Management, Northwestern University. I am also the Director of the Program on Healthcare at Kellogg. At Kellogg, I teach courses in the economics of strategy and health care strategy and organize Kellogg's healthcare business curriculum. In addition, I am a Research Associate at the National Bureau of Economic Research, and a Faculty Associate at the Institute for Policy Research at Northwestern University.

22. I received a PhD in Economics from the University of Maryland at College Park, a Master's in Public Policy from the Gerald R. Ford School of Public Policy at the University of Michigan, and a B.A. in Political Science from the University of Michigan.

23. Prior to my graduate studies, I was an Economist at Public Sector Consultants in Lansing, MI, and the Director of Research and Chief Economist at the Employment Policies Institute, in Washington, DC.

24. My research focuses on the business of healthcare with a focus on the interaction between private firms and public policies. My recent work has studied pricing and innovation in the biopharmaceutical sector. In this area, I have examined the effect of changes in market size of investments in new product development, the evolving world of precision medicine, the innovation response of United States pharmaceutical firms to increases in demand, and the relationship between health insurance expansions and drug prices, among others.

25. My research has been published in journals such as the *Quarterly Journal of Economics*, the *American Economic Review*, the *Review of Economics and Statistics*, the *Journal of Health Economics*, the *New England Journal of Medicine*, the *Annals of Internal Medicine*, and *Health Affairs* and has been profiled in media outlets such as the New York Times, the Wall Street Journal, the Washington Post, and Vox. I have testified before the United States Senate, United States House of Representatives and state legislatures on matters related to health care reform, pharmaceutical markets, and minimum wage.

26. A copy of my curriculum vitae is attached as Appendix A to this report and includes a list of my publications authored in the previous ten years. Appendix B includes a list of cases in which I have testified either at deposition or trial within the last four years, and recent testimony before Congress.

II. BACKGROUND

A. Innovation in the biotechnology and pharmaceutical industry

27. Biopharmaceutical innovation has led to cures for diseases that used to be debilitating or fatal. For example, biopharmaceutical innovation has reduced mortality or morbidity in diseases such as HIV,[22] Hepatitis C,[23] and cancer.[24] Life expectancy in the U.S. increased

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[22] Philipson, T.J. and Jena, A.B., "Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs," Forum for Health Economics & Policy (Vol. 9, No. 2), 2006.

[23] Lam, B et al., "The Changing Landscape of Hepatitis C Virus Therapy: Focus on Interferon-Free Treatment," Therapeutic Advances in Gastroenterology, Vol. 8 (5), 2015.

[24] See Lakdawalla, D et al., "An Economic Evaluation of the War on Cancer," Journal of Health Economics 29(3), 2010, at 333-346.

by 3.3 years between 1990 and 2015; estimates suggest that 35 percent of this increase is attributable to drug innovation.[25]

28. Biopharmaceutical innovations are not a thing of the past. For example, chimeric antigen receptor (CAR) T-Cell therapy are a new and major advancement in cancer treatment. In CAR T-Cell therapy, a patient's immune system (specifically the patient's T-Cells) is genetically engineered to fight cancer.[26] CAR T-Cell therapy, approved by the U.S. Food and Drug Administration (FDA) in 2017, has been particularly effective in treating acute lymphoblastic leukemia (ALL), the most common form of childhood cancer. For patients with recurrent ALL, which was previously untreatable, CAR T-Cell therapy has led to remission rates of up to 90%.[27,28] CAR T-Cell therapy is also effective against other types of cancer, such as advanced lymphoma.[29] Other significant advances in gene therapy include treatment of sickle-cell disease, a blood disorder that affects 90,000 people in the U.S;[30] inherited mutations that can cause blindness;[31] and hemophilia.[32]

29. These advances are the result of decades of costly R&D investments by the biopharmaceutical industry and other partners. At the time at which biopharmaceutical

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25 Buxbaum, J et al., "Contributions Of Public Health, Pharmaceuticals, And Other Medical Care To US Life Expectancy Changes, 1990-2015," Health Affairs 2020 39:9, 2020, at 1546-1556.

26 NIH National Cancer Institute, "CAR T Cells: Engineering Patients' Immune Cells to Treat Their Centers," July 30, 2019 (https://www.cancer.gov/about-cancer/treatment/research/car-t-cells).

27 Maude, S et al., "Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia," New England Journal of Medicine, Vol. 371 (16), October 16, 2014.

28 NIH National Cancer Institute, "CAR T Cells: Engineering Patients' Immune Cells to Treat Their Centers.," July 30, 2019 (https://www.cancer.gov/about-cancer/treatment/research/car-t-cells).

29 NIH National Cancer Institute, "CAR T Cells: Engineering Patients' Immune Cells to Treat Their Centers.," July 30, 2019 (https://www.cancer.gov/about-cancer/treatment/research/car-t-cells).

30 Ribeil, JA et al., "Gene Therapy in a Patient with Sickle Cell Disease," New England Journal of Medicine, Vol. 376 (9), March 2, 2017.

31 FDA, "FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss," December 18, 2017 (https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss).

32 Rangarajan, S et al., "AAV5-Factor VIII Gene Transfer in Severe Hemophilia A," New England Journal of Medicine, Vol. 377 (26), December 28, 2017.

companies invested in them, these were risky efforts to expand and commercialize scientific knowledge. In this section, I describe the regulatory and market institutions that facilitate and reward these risky investments. I describe how the drug development and approval process works in the U.S., how biotechnology firms decide how much and where to invest, and what role expected prices play in investment decisions.

1. The drug development process

30. There are two broad categories of drugs in the FDA approval process: "innovator" drugs and generic or biosimilar drugs. Innovator drugs require years of research, development, testing, and trials before they gain approval for sale in the U.S.[33] In contrast, generic drugs are approved in a much faster process through an abbreviated drug application (ANDA) which must only prove the generic drug contains the same active ingredient and is comparable on a number of different dimensions (e.g., dosage form, strength, route of administration, intended use) to the innovator drug.[34] Similarly, an abbreviated process developed through the Biologics Price Competition and Innovation Act is also available for biosimilar drugs.[35] Through this process, biosimilar manufacturers can bypass the requirement to conduct equally lengthy and costly clinical trials to the innovator biologic product by showing that the biosimilar product is "highly similar to, and has no clinically meaningful differences… from an existing FDA-approved reference product."[36] The data used to compare the biosimilar to the innovator biologic can include analytical (structural and functional) characterization, animal studies (if necessary), and comparative clinical

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33 Torjesen, I, "Drug Development: The Journey of a Medicine from Lab to Shelf," The Pharmaceutical Journal, PJ March 2015 (https://www.pharmaceutical-journal.com/test-tomorrows-pharmacist/tomorrows-pharmacist/drug-development-the-journey-of-a-medicine-from-lab-to-shelf/20068196.article).

34 FDA, "Abbreviated New drug Application (ANDA)," viewed December 3, 2020 (https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda).

35 FDA, Patient Protection and Affordable Care Act Title VII, Subtitle A, §§7001-7003 (https://www.fda.gov/media/78946/download).

36 FDA, "Biosimilar Development, Review, and Approval," October 20, 2017 (https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval).

studies involving human subjects.[37] Thus, companies developing innovator drugs bear the risk and expense of drug development, but are investing in the potential health care advances of the future.

31. The process companies developing innovator drugs must complete are daunting, and the odds that research on a candidate drug are successful are slim. It is estimated that only one out of every five to ten thousand compounds researched during the first phase of drug development (i.e., drug discovery) wins FDA approval,[38] and the entire development process can take as long as 15 years.[39] In general, the drug development process follows the steps described below and summarized in **Figure 1**:

- ***Drug discovery and preclinical trials*** - the primary goal of this first step is to determine if the drug is reasonably safe for initial use in humans, and if the drug exhibits pharmacological activity that would justify commercial development. This first step takes three to six years.[40] Upon completion, an Investigational New Drug application (IND) is submitted to the FDA for approval and the formal FDA review process is started.[41] Less than one in one thousand candidate compounds make it through this first step.[42]

- ***Clinical trials*** - once the formal FDA review process is started, human clinical trials may begin. These trials include three phases (i.e., Phase I, Phase II, and Phase III), each of which require compliance with rigorous guidelines and ethical safeguards

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37 FDA, "Biosimilar Development, Review, and Approval," October 20, 2017 (https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval).

38 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 37.

39 Downing N., "Promoting Innovation in Drug Development", Yale University, viewed December 3, 2020 (https://isps.yale.edu/news/blog/2014/02/promoting-innovation-in-drug-development). See also, The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 37.

40 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 35. (https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application).

41 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 37.

42 FDA, "The Beginnings: Laboratory and Animal Studies", viewed December 8, 2020 (https://www.fda.gov/drugs/information-consumers-and-patients-drugs/beginnings-laboratory-and-animal-studies).

that must be met to ensure patient safety and reduce the likelihood that patients receive treatments that are less effective than available alternatives.[43] Phase I typically involves 20 to 80 patients; this phase evaluates how the drug is metabolized and acts as a preliminary test for safety. [44] Phase II involves hundreds of patients and tests for safety, efficacy, dosage form, and the appropriate duration.[45,46] 74 percent of new molecular entities and 66 percent of biologics are unsuccessful in Phase II.[47] Finally, Phase III involves thousands of patients and performs further tests of safety and efficacy. [48] In total, moving through the three phases of clinical trials can take six to seven years.[49] Upon completion, a New Drug Application (NDA) or Biologics License Application (BLA), dependent on how the drug is derived, is submitted to the FDA for approval.[50] In total, only 6.2% of new molecular entities and 11.5% of biologics that entered Phase I trials ultimately gain FDA approval.[51] Even for drugs that reach Phase III, only about half of them will ultimately gain FDA approval.[52]

- ***Manufacturing and post-market surveillance*** - Once the drug is available to consumers, the manufacturer must submit periodic safety reports to the FDA. These

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43 Umscheid, CA et al., "Key Concepts of Clinical Trials: A Narrative Review," Postgraduate Medicine Vol. 123 (5), September, 2011.

44 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 35.

45 FDA, "Step 3: Clinical Research," viewed December 8, 2020 (https://www.fda.gov/patients/drug-development-process/step-3-clinical-research).

46 FDA, "Clinical Pharmacology 2: Clinical Pharmacology Considerations During Phase 2 and Phase 3 of Drug Development," viewed December 8, 2020 (https://www.fda.gov/media/84924/download).

47 Biotechnology Innovation Organization, "Clinical Development Success Rate 2006-2015," June 2016, at 20.

48 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 36.

49 PhRMA, "Biopharmaceutical Research & Development: The Process Behind New Medicines," viewed December 8, 2020 (http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf).

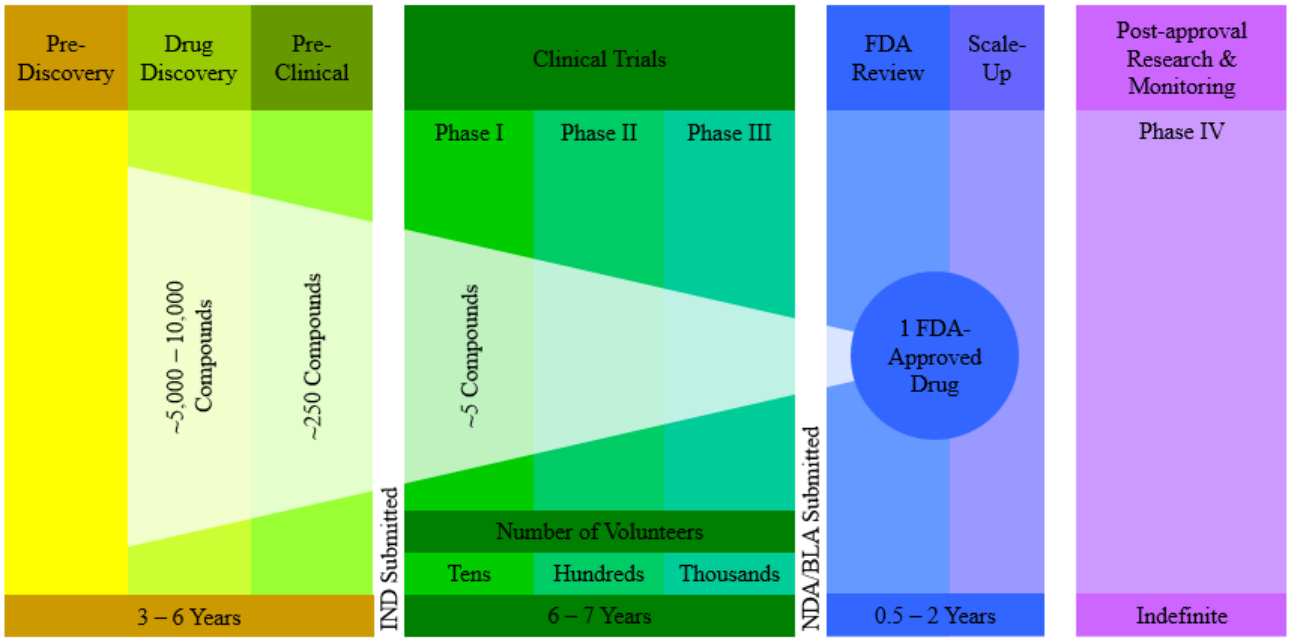
50 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 36. See also, Alabanza, A., M.S., R.A.C., "What are the Regulatory Differences Between an NDA and BLA?" Nuventra, viewed December 8, 2020 (https://www.nuventra.com/resources/blog/regulatory-differences-between-an-nda-bla/).

51 Biotechnology Innovation Organization, "Clinical Development Success Rate 2006-2015," June 2016, at 20.

52 Biotechnology Innovation Organization, "Clinical Development Success Rate 2006-2015," June 2016, at 20.

periodic safety reports include information on reported side effects for the drug and, importantly, may flag whether a drug has side effects that were too uncommon to detect during clinical trials.[53]

Figure 1: The Drug Development Process of Innovator Drugs[54]



32. Researchers have confirmed that one consequence of this long and risky development process is that the average cost of bringing a new drug to market is high. In a sample of more than 100 investigational drugs initiated between 1995 and 2007 that enter clinical trials, DiMasi et al. (2016) find that almost 80 percent never enter Phase III, and that fewer than 12 percent receive FDA approval.[55] While the study by DiMasi et al. (2016) did include a small sample of biologics, the authors did not distinguish between small molecules and biologics. However, earlier research by DiMasi and Grabowski (2007)

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53 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 36.

54 The National Academies Press, "Making Medicines Affordable: A National Imperative," 2018, at 37. See also, PhRMA, "Biopharmaceutical Research & Development: The Process Behind New Medicines," viewed December 8, 2020 (http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf).

55 DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

found that biologics that are in phase I have a higher, but still low, probability of being brought to market: 30 percent for biologics compared to 21.5 percent for small molecules.[56]

33. Decreases in the likelihood of approval have been accompanied by increases in the costs of bringing a drug to market, which include the costs incurred on drugs that are not successfully brought to market. DiMasi et al. (2016) estimated that the total capitalized cost of bringing a drug to market is almost $2.6 billion.[57,58] This figure is the sum of $1.1 billion spent on pre-human trials and $1.5 billion spent on clinical trials and accounts for the fact that only 11.83 percent of investigational drugs are approved by the FDA. Including post-marketing studies increases the total cost to almost $2.9 billion. Pre-marketing drug development costs have grown at a rate of about 8.5 percent when compared to a previous study by the same authors of drugs initiated between 1983 and 1994.[59] Drug development costs are incurred disproportionally throughout the R&D process, with higher costs associated with the large-scale trials of Phase III, which are more than ten times as much as average Phase I costs.[60] DiMasi and Grabowski (2007) showed that on average, biologics took longer to develop, with a mean clinical development time of 98 months for biologics compared to 90 months for all drugs.[61] Based on subsequent

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56 DiMasi, J. and Grabowski H., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics, 2007. As the authors acknowledge, this success rate is substantially higher than the rate they estimate in their most recent study, but the more recent estimate is consistent with several recent studies of clinical success rates. DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

57 The capitalized cost is the sum of actual cash outlays plus time costs, i.e., the foregone value from not investing the money elsewhere. DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

58 Some recent alternative estimates are lower, but still substantial. For example, relying on a sample of ten companies' R&D spending, Prasad et al. (2017) estimate a median cost of developing a cancer drug of $648 million. Prasad V, Mailankody S., "Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval," JAMA Intern Med., 2017.

59 DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

60 DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

61 DiMasi, J. and Grabowski H., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics, 2007.

research, drug discovery and preclinical trials are longer and more costly for biologics than small molecule drugs, and clinical trials are shorter and less costly for biologics than small molecule drugs.[62]

34. An earlier systematic review of the literature on drug development costs found that the estimated cost of bringing a drug to market was between $185 million and $2.1 billion (converted to 2017 dollars).[63,64,65] Importantly, the lower end of this range consists of drugs initiated earlier in time (e.g., 1963 to 1975), whereas estimates at the higher end of the range come from more recent drug developments.[66] For drugs initiated after 1975, the range was $490 million to $2.09 billion with a median of $1.58 billion (converted to 2017 dollars).[67] The estimates from DiMasi and coauthors' 2003 study, which rely on the same methods as their 2016 study, fall within this range ($1.15 billion in 2017 dollars).[68,69,70]

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62 Grabowski, H. et al., "The Market For Follow-On Biologics: How Will It Evolve?" Health Affairs, 2006; Grabowski, H., "Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition," Nature Reviews Drug Discovery, 2008.

63 Morgan, S. et al., "The Cost of Drug Development: A Systematic Review," Health Policy, 2011.

64 There are other studies that estimate lower costs of drug development, but these have not been peer reviewed and contain numerous flaws. For example, in Public Citizen's 2001 report, they calculate total domestic R&D costs for only a subset of drugs and divide it by the total number of approved New Drug Applications ("NDAs"). Using a subset of R&D costs artificially deflates the numerator, and dividing by the number of NDAs inflates the denominator, therefore deflating the total cost estimate. Additionally, the Public Citizen (2001) study ignores time costs (i.e., the opportunity cost of capital), arguing that R&D spending is an expense and not an investment, which substantially reduces the estimated cost of drug development.

65 "CPI Inflation Calculator," U.S. Bureau of Labor Statistics.

66 Morgan, S. et al., "The Cost of Drug Development: A Systematic Review," Health Policy, 2011.

67 Morgan, S. et al., "The Cost of Drug Development: A Systematic Review," Health Policy, 2011. One hypothetical estimate for the cost of developing a Tuberculosis drug is excluded from this range.

68 DiMasi, J. et al., "The Price of Innovation: New Estimate of Drug Development Costs," Journal of Health Economics, 2003.

69 DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

70 "CPI Inflation Calculator," U.S. Bureau of Labor Statistics.

Given the increasing trend in drug development costs over time, it is not surprising that DiMasi and coauthors' 2016 estimates are above this range.[71]

35. The U.S. has a legal and regulatory structure that is intended to balance the twin goals of giving innovators sufficient expected profits to incentivize drug development and ensuring the widespread availability of drug innovations.[72][73,74] This is the underlying premise of the U.S. patent system, which provides a time limited period of intellectual property protection. In addition, the U.S. has instituted other legislation, specific to the pharmaceutical industry, to attempt to balance these twin goals. The Hatch-Waxman Act was designed to provide innovator drugs with a period of exclusivity during which they would not face competition from generics and to promote vigorous competition from generics at the end of period of exclusivity.[75,76] Similarly, the Biologics Price Competition and Innovation Act of 2009 ("BPCIA") provides a 12-year exclusivity period for novel reference biologics (12.5 years for biologics with pediatric use) and a 1-year exclusivity period for the first biosimilar.[77]

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71 Some studies contend that the DiMasi and coauthors' estimates are inflated because they rely on data from a select group of pharmaceutical companies who responded to their survey, estimate pre-tax costs that are not adjusted for R&D tax deductions, and calculate costs per new molecular entity instead of per approved new drug application. These critiques fail to acknowledge that the data were validated by independent investigators (which was known to survey respondents at the time of the survey), that parts of the data were confirmed against other widely-used commercial databases, and that R&D tax deductions occurring today are at the expense of not amortizing those costs when profits are earned in the future. Light, D., "Misleading Congress About Drug Development," Journal of Health Politics Policy and Law, October 2007; DiMasi, J. et al., "Reply: Setting the Record Straight on Setting the Record Straight: Response to the Light and Warburton Rejoinder," Journal of Health Economics 24, 2005 at 1049-1053; DiMasi, J. et al., "Reply: Extraordinary Claims Require Extraordinary Evidence," Journal of Health Economics 24, 2005 at 1034-1044; DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

72 Wheaton J, "Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984", 35 Cath. U. L. Rev. 433, 1986

73 FDA, "Biosimilars Action Plan: Balancing Innovation and Competition," July 2018.

74 FDA/FTC, "Workshop on a Competitive Marketplace for Biosimilars," viewed December 9, 2020 (https://www.federalregister.gov/documents/2020/02/04/2020-02101/food-and-drug-administrationfederal-trade-commission-workshop-on-a-competitive-marketplace-for).

75 Public Law 98-417, September 24, 1984.

76 Kelly, C., "The Balance Between Innovation and Competition: The Hatch-Waxman Act, the 2003 Amendments, and Beyond," Food and Drug Law Journal, Vol. 66, no. 3, 2011.

77 FDA, Patient Protection and Affordable Care Act Title VII, Subtitle A, §§7001-7003 (https://www.fda.gov/media/78946/download).

During the period of exclusivity, makers of innovator drugs and reference biologics have an opportunity to recoup their investment. Without this period of exclusivity, there is little incentive to develop an innovator drug, because competition from generics and biosimilars would prevent the innovator drug from earning enough in profits to cover the fixed costs of drug development.[78] The patent system gives innovator drugs 20 years of protection from the time of patent filing. [79] Given that the entire development process can take as long as 15 years, this equates to an effective remaining patent life of as little as five years at the time of FDA approval.[80,81] The relatively short period of exclusivity for innovator drugs, along with typically declining revenues after loss of exclusivity, means that the markups and revenues on patented drugs must be high if drug manufacturers can reasonably expect to recoup their investments and therefore are willing to make such large, fixed, and sunk investments in the first place. It also means that the loss to consumers from high returns to manufacturers occurs over a relatively short time span, and any reduced social welfare from a lower quantity sold is also over a relatively short time period. In addition, these losses from a lower quantity sold are partially mitigated by the existence of health insurance products that shield consumers from the full burden of high prices.[82]

36. Because new drugs enter the market with high prices and revenues but typically see them fall after patent expiration, the growth rate in U.S. spending on drugs varies over time with the life cycle of drugs that are on the market. In periods of increased innovation during which many new drugs come to market, the growth rate in U.S. drug spending increases

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78 Morgan M, "Regulation of Innovation under Follow-On Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanisms," Colum. Sci. & Tech. L. Rev. 93, 2010

79 FDA, "Frequently Asked Questions on Patents and Exclusivity," viewed December 11, 2020 (https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#howlongpatentterm).

80 Berger, J. et al., "How Drug Life-Cycle Management Patent Strategies May Impact Formulary Management," Am J Manag Care, Vol. 22, no. 16, October 1, 2016.

81 Drugs may be eligible for patent-term extension. For example, in a sample of 170 top-selling drugs approved between 2000 and 2012, roughly half received a patient extension. The median extension was 2.75 years. See Reed F. Beall et al., "Patent Term Restoration for Top-Selling Drugs in the United States," Drug Discovery Today, Volume 24, Issue 1, 2019.

82 Lakdawalla, Darius, Neeraj Sood, "Health Insurance as a Two-Part Pricing Contract," Journal of Public Economics, 2013.

due to both increased demand for drugs and high prices. When those drugs lose market exclusivity, competition from generics and biosimilars pushes down prices and revenues. U.S. patients benefit from both access to new drugs and from price decreases on these drugs when they eventually lose market exclusivity or face competition from therapeutic substitutes. However, the salience of drug pricing has grown over time likely as a result of higher consumer cost sharing and also may be highest during periods of intense drug innovation where products generating the most consumer value are able to charge the highest prices during periods of market exclusivity.

37. While the period from 2005 through 2013 was one in which drug spending growth was slow in part because of the loss of exclusivity for a number of blockbuster drugs, 2014 was a year of fast spending growth because of the entry of new drugs.[83] The increasing rate of new drug innovation in 2014 and subsequent years has been driven by a revolution in medicine resulting from the development of new types of drugs called "biologics."[84] Historically, most drugs were small, chemically manufactured molecules that create therapies synthesized by chemical reactions between different organic and/or inorganic compounds (i.e., small molecule drugs). In comparison, biologics or "biologic therapy," are large molecules derived from the extraction or manipulation of living organisms. [85] The first biologic approved for therapeutic use was biosynthetic "human" insulin in 1982.[86] Other examples of biologics include monoclonal antibodies, vaccines, blood and blood

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83 Aitken, M. et al., "Has The Era Of Slow Growth For Prescription Drug Spending Ended?" Health Affairs, Vol. 35, No. 9, Sept 2016, at 1595-603.

84 Munos, Bernard, "2014 New Drug Approvals Hit 18-Year High," viewed December 11, 2020 (https://www.forbes.com/sites/bernardmunos/2015/01/02/the-fda-approvals-of-2014/?sh=6b8b5e0a3118). Owens, Gary M., "New FDA Drug Approvals Hit an 18-Year High in 2014." American Health & Drug Benefits vol. 8 (Spec Feature), 2015.

85 Lybecker, K. M., "The Biologics Revolution in the Production of Drugs," Fraser Institute, July 2016. See also, Evens, R. and Kaitin, K., "The Evolution Of Biotechnology And Its Impact on Health Care," Health Affairs, Vol. 34, No. 2, 2015, at 210-219.

86 U.S. Pharmacist, "The Use of Biologics in Cancer Therapy," viewed December 3, 2020 (https://www.uspharmacist.com/article/the-use-of-biologics-in-cancer-therapy).

products, protein hormones, cellular therapies, allergenic extracts, and gene therapy products.[87]

38. Today, biologics represent over a third of net drug spending.[88] At least three factors, as described below, contribute to biologics' growing share of spending: they are expensive to manufacture, are innovative options that tend to treat serious or previously untreatable diseases, and account for a growing share of new drug approvals.

39. Biologics are more difficult, complex, and expensive to manufacture than small molecule drugs, because biologics are highly sensitive to the conditions in which they are manufactured and handled, whereas small molecule drugs can be manufactured by chemical synthesis. Even minor differences in biologic production processes can generate variations in the resulting protein.[89]

40. The pharmaceutical industry has been revolutionized by biologics, in part, because these products have been shown to have greater on-target efficiency and lower off-target toxicity relative to traditional small molecule drugs.[90] Notably, many biologics treat cancer by "targeting" cancer cells without affecting normal cells.[91] Targeted therapies are often safer and have fewer side effects than older chemotherapy drugs, which kill both cancer and normal cells.[92] In addition, biologics often target conditions for which there was previously

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87 Lybecker, K. M., "The Biologics Revolution in the Production of Drugs," Fraser Institute, July 2016.

88 Washington Examiner, "When Cost Saving is Lifesaving: Expanding Patient Access to Biosimilars," viewed December 3, 2020 (https://www.washingtonexaminer.com/opinion/when-cost-saving-is-lifesaving-expanding-patient-access-to-biosimilars).

89 Lybecker, K. M., "The Biologics Revolution in the Production of Drugs," Fraser Institute, July 2016.

90 Lybecker, K. M., "The Biologics Revolution in the Production of Drugs," Fraser Institute, July 2016.

91 American Cancer Society, "How Targeted Therapies Are Used to Treat Cancer," viewed December 4, 2020 (https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/targeted-therapy/what-is.html). See also, Arizona Oncology, "Biologic and Targeted Therapies," viewed December 4, 2020 (https://arizonaoncology.com/cancer-treatments/targeted-therapy).

92 American Cancer Society, "How Targeted Therapies Are Used to Treat Cancer," viewed December 4, 2020 (https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/targeted-therapy/what-is.html). See also, Arizona Oncology, "Biologic and Targeted Therapies," viewed December 4, 2020 (https://arizonaoncology.com/cancer-treatments/targeted-therapy); American Cancer Society, "How

substantial unmet need or managed only symptomatically.[93] For example, biologics are more likely than small molecule drugs to treat rare disease (as designated by FDA "orphan drug" status).[94]

41. In fact, biologics have grown from 20 percent of FDA approvals for new drugs, for the five-year period of 2010 to 2014, to 28 percent for the five-year period of 2015 to 2019.[95] In addition, several pharmaceutical firms have set explicit targets for the biologics share of their research pipeline ranging from 20 percent to more than 75 percent.[96]

42. Biotechnology ("biotech") firms are those firms that produce biologics. In some cases, these are established pharmaceutical companies and in other cases, small start-ups.[97] The number of biotech firms has grown dramatically; in the 1980s, only a handful of U.S. biotech companies existed, and by 2000, there were more than 4,600 biotech firms globally.[98]

43. Small biotech firms in particular are critical to the advancement of biologics and account for the vast majority of drugs in clinical trials. For example, as of March 2018, 70 percent

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Chemotherapy Drugs Work," viewed December 4, 2020 (https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-chemotherapy-drugs-work.html).

93 Evens, R. and Kaitin, K., "The Evolution Of Biotechnology And Its Impact on Health Care," Health Affairs, Vol. 34, No. 2, 2015, at 210-219.

94 FDA, "Designing an Orphan Product: Drugs and Biological Products," viewed December 4, 2020 (https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products). For a sample of drugs launched in the US between 1998Q1 and 2008Q4, 24 percent of biologics received Orphan drug designation, whereas only 13 percent of small molecule drugs received orphan status. Trusheim, M. R., et al., "Characterizing Markets for Biopharmaceutical Innovations: Do Biologics Differ from Small Molecules?" Forum for Health Economics & Policy, 2010, at 25.

95 de la Torre, B. G. et. al., "The Pharmaceutical Industry in 2019. An Analysis of FDA Drug Approvals from the Perspective of Molecules," MDPI, Molecules 2020, Vol 25, No. 745, February 9, 2020.

96 Lybecker, K. M., "The Biologics Revolution in the Production of Drugs," Fraser Institute, July 2016.

97 Evens, R. and Kaitin, K., "The Evolution Of Biotechnology And Its Impact on Health Care," Health Affairs, Vol. 34, No. 2, 2015, at 211.

98 Evens, R. and Kaitin, K., "The Evolution Of Biotechnology And Its Impact on Health Care," Health Affairs, Vol. 34, No. 2, 2015, at 213.

of innovator drug clinical trials were led by small biotech firms, 40 percent of which were for oncology.[99]

2. Investment decisions

44. Biotech is a high-growth, high-risk industry. Biotech investments are typically expected to lose money in the short- and medium-term, as firms develop products, and only attain profitability in the long-term for firms that are successful in these earlier stages (see Section II.A.1). Despite high long-term returns for those biotech firms that succeed in developing a drug, most are not successful even in the long-term, and therefore the biotech industry is not, on average, highly profitable.[100] Despite these headwinds, successful biotech firms must have financing strategies that preserve their access to needed funding in the short- and medium-term to cover their losses while they pursue R&D. This funding comes from investors that are acutely aware that most biotech investments do not pay off and who are sensitive to both changes in expected odds of success and the magnitude of the rewards for successful products when deciding whether to continue funding a biotech firm.[101]

45. Investment decisions vary based on the size of the biotech firm. Large biotech firms and established pharmaceutical companies ("large biotech firms") are typically public companies that engage in a wide range of activities, such as R&D, large-scale production, marketing, and distribution. Large biotech firms have a portfolio of drugs that may include both small molecule drugs and biologics; these firms allocate resources across projects to achieve maximum risk-adjusted returns.[102] In addition, many of these firms have expertise

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99 Source defines small biotech firms as those below $1 billion in sales. BIO, "The Biotechnology Ecosystem: By The Numbers," (https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO_Ecosystem_Infographic_r9.pdf). See also, Thomas, D., CFA, and Wessel, C., "Emerging Therapeutic Company Investment and Deal Trends", BIO Industry Analysis, May 17, 2018.

100 Thakor, RT et al.,"Just How Good an Investment is the Biopharmaceutical Sector?" Nature Biotechnology, 35(12), 2017.

101 Thakor, RT et al.,"Just How Good an Investment is the Biopharmaceutical Sector?" Nature Biotechnology, 35(12), 2017.

102 Investopedia, "Pharmaceutical Vs. Biotech Investing: Is it Worth The Risk?" viewed December 4, 2020 (https://www.investopedia.com/articles/general/022814/pharmaceutical-vs-biotech-investing-it-worth-risk.asp).

of the regulatory process required to bring products to the market and the substantial resources required to do so.[103] If these large biotech firms need to raise capital, they often do so through the public market.[104]

46. Small biotech firms, which in 2017 accounted for 70 percent of biologics in the global drug development process, typically focus on R&D for a small number of drugs.[105] The strategy for many of these firms is to develop a biologic with the ultimate goal of being acquired by a large pharmaceutical company that will be able to operationalize their growth strategy and bring the drug to market.[106] In fact, one study found that by 2014, 190 biotech firms had been acquired by larger pharmaceutical companies totaling almost $400 billion in acquisition prices.[107]

47. Prior to acquisition, many of these small biotech firms rely on venture capital, angel investments, grants, and/or partnerships with large biotech firms for capital raising, which may depend on the firm's stage of development.[108]

48. Capital raising for small biotech firms is incredibly complex in part, for two reasons: (i) "standard" valuation multiples are less relevant as these firms do not have revenues, let

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103 Audretsch, D. B., et al., "Small-Firm Strategic Research Partnerships: The Case of Biotechnology," Technology Analysis & Strategic Management, Vol. 15, No. 2, 2003.

104 Booth, Bruce, "The Incredible Expanding Universe of Biotech Stocks," September 21, 2018, viewed December 11, 2020 (https://www.forbes.com/sites/brucebooth/2018/09/21/the-incredible-expanding-universe-of-biotech-stocks/?sh=2b73a2be9bd6).

105 Investopedia, "Pharmaceutical Vs. Biotech Investing: Is it Worth The Risk?" viewed December 4, 2020 (https://www.investopedia.com/articles/general/022814/pharmaceutical-vs-biotech-investing-it-worth-risk.asp).

106 Thakor, RT et al., "Just How Good an Investment is the Biopharmaceutical Sector?," Nature Biotechnology, 35(12), 2017; Tyebjee T, Hardin J., "Biotech-Pharma Alliances: Strategies, Structures and Financing," Journal of Commercial Biotechnology, Volume 10(4), 2004.

107 Evens, R. and Kaitin, K., "The Evolution Of Biotechnology And Its Impact on Health Care," Health Affairs, Vol. 34, No. 2, 2015, at 211.

108 Source defines small biotech firms as those below $1 billion in sales. BIO, "The Biotechnology Ecosystem: By The Numbers," (https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO_Ecosystem_Infographic_r9.pdf). See also, The Balance Small Business, "How to Finance a Biotech Start-up," viewed December 4, 2020 (https://www.thebalancesmb.com/top-suggestions-for-financing-a-startup-375549).

alone profitability or cash flow measures, and (ii) most will ultimately fail.[109] However, biotech firms can raise capital by offering the prospect for high returns in the rare event that they succeed.

49. Although obtaining funding is complex for small biotech firms, it is critical to their success and often the foremost focus of business operations of a start-up biotech company.[110] In fact, small biotech firms accounted for more than 50 percent of biotech capital raised each year from 2001 to 2016.[111] In addition, venture capital to the biotech industry has surged in recent years; in 2016, there were 673 U.S. biotech deals valued $9.4 billion, in 2019 there were 941 deals valued at $17.2 billion. In 2020, the number of deals has lagged slightly at 228 deals between February and mid-May, compared to 271 in the same period the prior year.[112] To put this in perspective, the capitalized cost of bringing a drug to market was an estimated $2.6 billion in 2016, comprised of $1.1 billion spent on pre-human trials and $1.5 billion spent on clinical trials.[113]

50. Each investor will have their own metrics and portfolio to consider when deciding how much to fund the R&D projects of small biotech firms. In general, metrics for biotech investment evaluation may include: (1) concept or how revolutionary the concept is, (2) science or how credible the experiments are, (3) management or how experienced the team is, (4) market or how big the addressable market is, (5) competition or how much competition the drug will have, (6) intellectual property or what type of intellectual

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109 Raphael Rottgen, "Biotech Valuation Idiosyncracies and Best Practices," viewed December 11, 2020 (https://www.toptal.com/finance/valuation/biotech-valuation).

110 Tsai, W. and Erickson, S., "Early-Stage Biotech Companies: Strategies For Survival and Growth," Biotechnology Healthcare, 2006.

111 Defined by E&Y report as those firms with revenues of less than $500 million. Ernst and Young, "Biotechnology Report 2017," at 57.

112 Biopharma Dive, "Venture Capital Found Its Footing in Biotech. Then Came the Virus," viewed December 4, 2020 (https://www.biopharmadive.com/news/venture-capital-biotech-coronavirus/577644/).

113 This estimate accounts for the fact that only 11.83 percent of investigational drugs are approved by the FDA. The capitalized cost is the sum of actual cash outlays plus time costs, i.e., the foregone value from not investing the money elsewhere. DiMasi, J. et al., "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," Journal of Health Economics, 2016.

property the firm must have such as composition of matter and/or method of use, (7) valuation or how the company may be valued, and (8) geography or whether to invest in a broad geography.[114] Investors typically prefer higher expected returns and less risk, all else equal, and continually re-evaluate their portfolio strategy within and across sectors.[115] Thus, if the expected return or risk on biotech investments changes, investors will shift funding accordingly.[116]

3. The role of expected prices in drug innovation

51. A number of academic articles illustrate that the amount and direction of pharmaceutical innovation is affected by expected profitability. Many of these articles study how innovation is affected by changes in potential "market size" (e.g., the number of patients a drug could potentially treat), which is an important determinant of expected profitability.

- Acemoglu & Linn (2004) find that a one percent increase in potential market size increases the number of new drugs by six percent.[117]
- Finkelstein (2004) finds that a one dollar increase annual expected market revenue increases R&D spending by six cents.[118]

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114 Agge, A. and Meyerson, G., "Biotech Venture Capital: The Investment Decision Process," The Journal of Private Equity, 2008.

115 Thakor, RT et al., "Just How Good an Investment is the Biopharmaceutical Sector?," Nature Biotechnology, 35(12), 2017.

116 "Unleashing the Next Generation of Biotechnology Innovation," viewed December 11, 2020 (http://www.bio.org/sites/default/files/legacy/bioorg/docs/Whitepaper-Final.pdf).

117 Acemoglu and Linn (2004) measure potential market size using demographic changes in the U.S. Acemoglu, D., and Linn, J., "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry," The Quarterly Journal of Economics Vol. 119, No. 3, 2004, at 1049-1090.

118 Finkelstein (2004) studies the effect of a policies designed to increase vaccination rates of specific diseases on R&D on vaccines for those diseases. Finkelstein, A.' "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," The Quarterly Journal of Economics, Vol. 119, No. 2, 2004, at 527-564.

- Yin (2008) finds that an income tax credit for 50 percent of clinical trial expenses, combined with a 7-year market exclusivity provision, increased clinical trials for a subset of disease by 69 percent.[119]
- Blume-Kohout & Sood (2013) find that that an increase in market size of one percent leads to an increase of between 2.4 percent and 4.7 percent for Phase I clinical trials, and 3.3 percent for all phases of clinical trials combined.[120]
- Dubois et al. (2015) find that a 10 percent increase in potential market size increases the number of new treatments in a given market by 2.3 percent.[121]
- In Dranove et al. (2020), my coauthors and I find that the introduction of Medicare Part D increased the number of clinical trials employing scientifically novel designs by 14 percent, and trials employing less-novel designs by between 84 and 106 percent.[122]

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[119] Yin (2008) studies the effect of the Orphan Drug Act, which incentivized the development of drugs for rare diseases through tax incentives and increased market exclusivity (that the author argues was offered little benefit beyond existing patent protection). He finds a 69 percent increase in clinical trials for "traditional" long–established "rare diseases" and a limited "increase in the stock of drugs in the years immediately subsequent to the ODA's passage [in the smallest markets]." He also finds a "232% […] increase in the rate of new clinical trials for more prevalent rare diseases relative to control diseases." Yin, W., "Market Incentives and Pharmaceutical Innovation," Journal of Health Economics, Vol. 27, No. 4, 2008, at 1060-1077.

[120] Blume-Kohout and Sood (2013) estimate the association between the number of clinical studies entering each stage of the R&D pipeline and pre-Part D Medicare market size following the passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which increased the potential market size for drugs prescribed to Part D patients. Blume-Kohout, M. E., and Sood, N. "Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development," Journal of Public Economics, Vol. 97, 2013, at 327-336.

[121] Dubois et al. (2015) estimate the association between the number of new chemical entities in a disease class market and the expected market size as measured by spending on treatment in the class. Dubois, P. et al., "Market Size and Pharmaceutical Innovation," The RAND Journal of Economics, Vol. 46, No. 4, 2015, at 844-871.

[122] In Dranove et al. (2020), my coauthors and I study the effect of an increase in expected profits resulting from the introduction of Medicare Part D on the novelty of firms' R&D investments. We measure novelty from the scientific perspective of whether a drug represents either the first application of a new molecular-targeting design, or the first combination of existing molecular-targeting designs, both of which are relatively risky endeavors that have the potential to create new therapeutic value even if they do not make it to market. Our results show that, while the increase in expected profits had the largest effect on less-novel trials, it did have a modest effect on novel designs, particularly those employing novel combinations of existing scientific approaches. We estimate that the increase in expected profits resulted in a 106 percent increase in the number

B. Healthcare systems

52. As noted above, the IFC includes a reference to drug prices charged in other countries. The healthcare systems of the countries included in the reference basket of the IFC share some similarities, but also vary materially in many dimensions. In many of these countries, a large majority (or all) of residents receive healthcare benefits through a tax-funded national healthcare system or a mandatory social health insurance, which include some form of pharmaceutical care. For example, in the UK, all residents are covered by centralized national ("single payer") healthcare systems, which are managed by the government.[123] Germany, on the other hand, has a private multi-payer system in which most residents are covered by not-for-profit "sickness funds."[124]

53. The health systems in these countries rely on a variety of instruments to decide whether to cover a given drug and how to determine its price. One instrument that is used in several European countries is the "health technology assessment" ("HTA"), a "multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner."[125] An HTA evaluates a drug's added therapeutic value relative to existing treatments, and its cost-effectiveness. In some countries, HTAs are used to determine drug

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of clinical trials for the least novel drugs and a 14 percent increase in trials involving the most innovative designs (i.e., the first application of a new molecular-targeting design). For drug trials employing combinations of existing molecular-targeting designs, we estimate an 84 percent increase in clinical trials for the least novel combinations and a 14 percent increase for the most novel combinations. Importantly, we note in the paper that it is unclear whether the effects from a larger change in market size might have disproportionate effects on novel drug development. Dranove, D. et al., "Expected Profits and the Scientific Novelty of Innovation," National Bureau of Economic Research, May 1, 2020.

123 Paris, V. and Belloni, A., "Value in Pharmaceutical Pricing," OECD Health Working Papers No. 63, 2013.

124 Lauterbach K. et al., "Germany's Model for Drug Price Regulation Could Work in the US," Health Affairs Blog, December 29, 2016, viewed October 5, 2020 (https://www.healthaffairs.org/do/10.1377/hblog20161229.058150 /full/).

125 WHO: Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, "PPRI Multilanguage Glossary of Pharmaceutical Terms," 2019, at 23, viewed December 11, 2020 (https://ppri.goeg.at/about_translations).

reimbursement levels, whereas in other countries HTAs are also used to approve or reject coverage of a drug altogether.[126]

54. Another instrument several countries use to inform reimbursement for drugs is "external price referencing" ("ERP"), the "practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country."[127] A 2015 study on the usage of ERP in 31 European countries found that 29 (94 percent) of them applied ERP to varying degrees.[128]

55. A central goal of these instruments is to control drug spending. For example, the UK National Health Service (NHS)'s ability and willingness to exclude a drug from its national formulary[129] provides it with leverage to demand lower prices from drug manufacturers.[130] Similarly, ERP allows countries to reimburse drug costs at levels that are more in line with other countries' prices.[131]

56. In contrast to these primarily government driven instruments used by other countries, in the U.S., private payers and drug manufacturers negotiate over drug prices. Private payers also compete with each other to provide insurance. Under the U.S. system, market forces

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126 Vogler, S. et al., "How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries," Appl Health Econ Health Policy, 15(3):307-321, 2017, Section II.

127 WHO: Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, "PPRI Multilanguage Glossary of Pharmaceutical Terms," 2019, at 23, viewed December 11, 2020 (https://ppri.goeg.at/about_translations).

128 Rémuzat, C. et al., "Overview of external reference pricing systems in Europe," Journal of Market Access & Health Policy, 3: 27675, 2015, at 1.

129 A formulary is a health plan's list of covered drugs. Department of Health and Human Services, "Formulary," viewed December 12, 2020 (https://www.healthcare.gov/glossary/formulary/).

130 National Institute for Health and Care Excellence, "Cancer Drugs Fund," viewed December 5 (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund). Maini, L. & Pammolli, F., "Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market," 2017, at 7.

131 Kanavos, P. et al., "The Impact of External Reference Pricing within and across Countries," London School of Economics and Political Science, 2017.

determine drug prices. The more competing treatments are available on the market, the easier it is for the payer to restrict access to the drug on its formulary, and the more leverage it has to negotiate a lower price for the drug. For highly valuable and innovative drugs with few or no alternatives, U.S. payers cannot credibly threaten to limit access to the drug on its formulary, because they compete with each other for patients. If any individual U.S. payer decides to not cover a drug in high demand, it may lose patients to competing payers. The provision of innovative drugs and competition among payers provides the drug manufacturer with the leverage to negotiate relatively higher prices.

57. The U.S. accounts for a large percent of global pharmaceutical sales and profits. The U.S. was estimated to account for 40 percent of global pharmaceutical sales in 2017.[132] By 2023, the U.S. is expected to account for 44 percent of global pharmaceutical sales.[133] This growth is fueled in part, by the growing and aging U.S. population. In 2000, 12.4 percent of the U.S. population was 65 years or older; by 2019 this figure reached 16.5 percent and is expected to exceed 21 percent by 2040.[134] In addition, U.S. consumers are estimated to account for 64 to 78 percent of total pharmaceutical profits.[135] This share is higher than the U.S.'s share of global sales because of higher use of newer and higher-strength drugs, as well as higher prices, in the U.S.[136] Thus, the U.S. is a key driver of innovation to the extent

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132 NAVADHI Market Research, "U.S. Pharmaceuticals Industry Analysis and Trends 2023," viewed December 10, 2020 (https://www.reportlinker.com/p05761205/U-S-Pharmaceuticals-Industry-Analysis-and-Trends.html?utm_source=GNW).

133 NAVADHI Market Research, "U.S. Pharmaceuticals Industry Analysis and Trends 2023," viewed December 10, 2020 (https://www.reportlinker.com/p05761205/U-S-Pharmaceuticals-Industry-Analysis-and-Trends.html?utm_source=GNW).

134 Statista, "Share of Old Age Population (65 Years and Older) in the Total U.S. Population from 1950 to 2050," viewed December 4, 2020 (https://www.statista.com/statistics/457822/share-of-old-age-population-in-the-total-us-population).

135 Goldman, D., Lakdawalla, D., "The Global Burden of Medical Innovation," USC Schaeffer, 2018, at 1.

136 Danzon, PM, Furukawa, MF, "International Prices and Availability of Pharmaceuticals in 2005," Health Affairs (Millwood), Volume 27(1), 2008 Jan-Feb; Goldman, D and Lakdawalla, D, "The Global Burden of Medical Innovation," 2018, viewed December 11, 2020 (https://www.brookings.edu/research/the-global-burden-of-medical-innovation/).

that global biopharmaceutical companies are forecasting and relying on large returns in the U.S. when making R&D investment decisions.

C. The role of Medicare Part B in the biotechnology and pharmaceutical value chain

58. Medicare is the federal health insurance program for those who are 65 or older and for certain disabled people who are under 65 in the U.S.[137] Effectively all individuals 65 or older in the U.S. have health insurance, and over 95 percent of them receive that coverage through Medicare.[138] Roughly 60 million people are enrolled in Medicare, and Medicare accounts for roughly 20 percent of healthcare spending in the U.S.[139] Benefits are administered through three different parts: Medicare Part A covers most inpatient care, Medicare Part B covers most physician and outpatient care, and Medicare part D covers retail prescription drugs.[140]

59. Medicare Part B covers drugs that are administered in physician offices or hospital outpatient departments.[141] Medicare Part B typically covers drugs for their FDA labeled indications and may also cover drugs for other indications for which the drug has not yet received FDA approval if those uses are deemed reasonable and necessary for the treatment of a disease.[142]

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137 Kaiser Family Foundation, "An Overview of Medicare," 2019, viewed December 11, 2020 (https://www.kff.org/medicare/issue-brief/an-overview-of-medicare/), at 1.

138 U.S. Census Bureau, American Community Survey, Table HI05_ACS Health Insurance Coverage Status and Type of Coverage by State and Age for All Persons: 2019, https://www2.census.gov/programs-surveys/demo/tables/health-insurance/2020/acs-hi/hi05_acs.xlsx.

139 Kaiser Family Foundation, "An Overview of Medicare," 2019, viewed December 11, 2020 (https://www.kff.org/medicare/issue-brief/an-overview-of-medicare/), at 1.

140 Roughly one-third of Medicare enrollees are enrolled in a Medicare Advantage plan in which a private insurer administers their benefits. Kaiser Family Foundation, "An Overview of Medicare," 2019, viewed December 11, 2020 (https://www.kff.org/medicare/issue-brief/an-overview-of-medicare/), at 3-4.

141 MedPAC, "Part B Drugs Payment Systems," 2019, viewed December 11, 2020 (http://medpac.gov/docs/default-source/payment-basics/medpac_payment_basics_18_partb_final_sec.pdf) ("MedPAC Part B Drugs Payment Systems"), at 1.

142 MedPAC Part B Drugs Payment Systems, at 1-2.

60. Under the Medicare Part B "buy and bill" system, providers (e.g., physicians) *buy* drugs from wholesalers, purchasing organizations, or manufacturers and then *bill* Medicare Part B for drugs that they administered to Medicare patients.[143] Medicare Part B typically reimburses providers for 106 percent of the average sale price ("ASP") of a drug.[144] This percentage was reduced to 104.3 percent in 2013, after Congress failed to pass a budget and a sequestration was ordered.[145] The ASP of a drug is calculated by manufacturers based on the net-of-discounts price at which they sell each drug in the U.S.[146] Not all providers purchase Part B drugs at the same price; some providers pay more than ASP, whereas other providers pay less than ASP for a drug.[147] Each provider earns a spread on drugs administered to Medicare patients, which is the difference between 106 percent of the ASP (i.e., what Medicare pays) and the price the provider paid for the drug. Therefore, providers have an incentive to pay lower prices for the drugs that they acquire, because doing so increases the spread that they can earn.

61. The economic rationale to Medicare's ASP pricing[148] is that the system is intended to compensate physicians for slightly more than their costs of acquiring drugs. For drugs that are predominantly attractive to privately insured patients, ASPs will generally reflect the valuations of drugs as determined by market forces within the U.S. More specifically, the price that physicians can charge the privately insured for a drug are dictated by the extent to which the privately insured value the drug. In turn, the price that physicians can charge will dictate the price that physicians are willing to pay for the drug. Finally, the price that

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143 ANPRM, at 54547-8.

144 MedPAC Part B Drugs Payment Systems, at 2.

145 Health Affairs Health Policy Brief Series, "Medicare Part B," 2017, viewed December 11, 2020 (https://www.healthaffairs.org/do/10.1377/hpb20171008.000171/full/), at 3.

146 When calculating ASP, manufacturers exclude sales to entities excluded from the calculation of Medicaid's best price. Therefore, ASP excludes "sales or discounts to other federal programs, 340B-covered entities, and state pharmaceutical assistance programs; rebates to Medicare Part D plans." MedPAC Part B Drugs Payment Systems, at 2, 4.

147 MedPAC Part B Drugs Payment Systems, at 3.

148 Some private payers also pay based on ASP. See Brookings, "The Use of Vendors in Medicare Part B Drug Payment," viewed December 10, 2020 (https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2019/08/02/the-use-of-vendors-in-medicare-part-b-drug-payment).

physicians are willing to pay for a drug will dictate the sales prices that pharmaceutical companies charge physicians for the drug (which average to ASP). By paying based on ASP, Medicare's prices provide innovation incentives, in terms of amount and direction of pharmaceutical innovation, that reflect the same priorities as market forces in the U.S. Medicare's pricing will also reflect the same prioritization of the trade-off between short term pricing and long-term innovation incentives as the private U.S. market.

62. For drugs that are largely sold to Medicare patients, ASPs largely reflect prices paid by physicians for Medicare patients. By selling a drug to physicians at a higher price, pharmaceutical companies can increase the drug's ASP and thus also the prices that Medicare will reimburse physicians for that drug. In turn, higher Medicare reimbursement rates increase the prices that physicians will be willing to pay for a drug. Thus, for drugs that are largely sold to Medicare patients, the ASP system can create upward pressure on drug prices that are not reflective of the preferences of the private market.[149] This creates additional incentives for investments in new products in these areas, beyond the level that would be supported by market forces for privately insured patients.

63. In general, many physician-administered drugs treat very serious illnesses. For example, 38 out of the 50 drugs (76 percent) for which Medicare Part B reimbursements would be reduced starting in January 2021 are commonly administered by oncologists and hematologists (i.e., doctors specializing in the treatment of cancer patients).[150] One of these drugs is Keytruda (pembrolizumab), a humanized antibody used to treat various types of cancer, such as lung cancer, melanoma, kidney cancer, and liver cancer. Of the 12 non-cancer drugs for which the reimbursements would be reduced starting in January 2021, four are commonly administered by rheumatologists and treat diseases such as rheumatoid

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149 Chandra, A., Garthwaite, C., "Economic Principles for Medicare Reform," The ANNALS of the American Academy of Political and Social Science, Vol. 686 (1), 2019, at 75-76; GAO, "Medicare Represented at Least Half of the Market for 22 of the 84 Most Expensive Drugs in 2015," 2017, at 1.

150 For 38 out of the 50 drugs included in year one of the MFN model, hematology/oncology is listed as one of the top 3 billing specialties. See CMS-5528-IFC, at 50-51.

arthritis, a disease in which the body's immune system typically attacks joints but may also attack organs.[151]

D. The interim final rule with comment period ("IFC")

64. The MFN model is implemented nationally for seven years, starting on January 1, 2021, i.e., six weeks after issuance of the IFC. It initially includes 50 selected Medicare Part B drugs, but this number will likely expand over time, as I discuss in Section III.C.

65. Participation in the MFN model is mandatory for all providers and suppliers (with limited exceptions) that participate in the Medicare program and submit separately payable claims for at least one of the included drugs.[152]

66. The Medicare payment amount for included drugs is set to "the lowest per capita Gross Domestic Product-adjusted (GDP-adjusted) price of any non-U.S. member country of the Organisation for Economic Co-operation and Development (OECD) with a GDP per capita that is at least sixty percent of the U.S. GDP per capita," and a fixed add-on payment amount per dose.[153]

67. The fixed add-on payment amount per dose is "calculated based on 6.1224 percent of historical applicable ASPs for 2019 final action claim lines for the selected MFN model drugs for the beginning of performance year 1."[154] For each quarter after Q1 2021, CMS

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[151] For four out of the 12 non-cancer drugs included in year one of the MFN model, rheumatology is listed as one of the top 3 billing specialties. See CMS-5528-IFC, at 50-51; Centers for Disease Control and Prevention, "Rheumatoid Arthritis," viewed December 4th, 2020 (https://www.cdc.gov/arthritis/basics/rheumatoid-arthritis.html).

[152] The IFC excludes certain types of providers, including children's hospitals, PPS-exempt cancer hospitals, critical access hospitals, some Indian Health Service Facilities, Rural Health Centers, Federally Qualified Health Centers, some hospitals paid based on reasonable costs, and extended neoplastic disease care hospitals. The IFC may also exclude certain hospitals that are participating in other CMMI demonstrations. See CMS-5528-IFC, at 19, 26.

[153] CMS-5528-IFC, at 7. "Dose" is defined as "the number of HCPCS billing units reported on a claim line." See CMS-5528-IFC, at 109.

[154] CMS-5528-IFC, at 109.

"will update the per-dose add-on payment amount using an inflation factor."[155] CMS calculates a fixed add-on payment amount per dose for Q1 2021 of $146.55.[156]

68. The MFN price is phased in over a period of four years. CMS will "phase-in the MFN Price by 25 percent per year for performance years 1 to 3 of the model, reaching 100 percent of the MFN Price for performance years 4 through 7 of the model."[157]

III. THE ECONOMICS OF THE NEW REGULATIONS IN THE IFC ARE MATERIALLY DIFFERENT THAN THOSE PROPOSED IN THE OCTOBER 2018 ANPRM

A. The IFC requires a mandatory, nationwide participation of Medicare participating providers and suppliers

69. The 2020 MFN model requires a "mandatory, nationwide participation of Medicare participating providers and suppliers (with limited exclusions)."[158]

70. The 2018 IPI Model, in contrast, proposed to include "all physician practices and hospital outpatient departments (HOPDs) that furnish the model's included drugs in the selected model geographic areas."[159] The purpose of having a selected number of geographic areas participate in the model was to "allow the Innovation Center to gain experience and insight into using an alternative payment methodology for drugs included in the model."[160] The plan was to select these geographic areas such that they "include 50 percent of Medicare Part B spending on separately payable Part B drugs."[161]

71. The purpose of the selection in the 2018 IPI Model was to be able to reliably evaluate the model: "Whenever feasible, a comparison group composed of entities similar to the model

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155 CMS-5528-IFC, at 109.

156 CMS-5528-IFC, at 112.

157 CMS-5528-IFC, at 84.

158 CMS-5528-IFC, at 29.

159 ANPRM, at 54552.

160 ANPRM, at 54553.

161 ANPRM, at 54553.

participants but not exposed to the model is used to determine the model impact. In this particular potential model, intervention and comparison groups would be determined through a random selection or assignment process."[162]

72. The IFC acknowledges that "there could be potential challenges associated with a mandatory, nationwide model, namely greater impacts on manufacturers, a greater number of MFN participants that potentially receive lower payments for drugs under the model, and fewer non-participants who potentially increase their patient volume should beneficiaries need to locate alternative sites of care,"[163] which are issues I discuss in Section V.

73. A nationwide, mandatory model does not allow for a reliable and rigorous evaluation that an experimental design would allow for. As the ANPRM stated in 2018, "[a] randomized design helps minimize the impact of unmeasurable factors that may contribute to providers' and suppliers' likelihood to participate in the model. Our inability to control for these unobserved differences could lead to biased or incorrect estimates in the evaluation of the model's impact on quality of care and spending."[164] I discuss this in more detail in Section IV.A.

B. The IFC describes an MFN price that differs substantially from the international pricing index in the ANPRM

1. In the IFC, drug reimbursement is calculated as the minimum international price, instead of the average price proposed in the ANPRM.

74. The process for calculating the reimbursement price in the ANPRM has changed materially in the IFC. Most notably, in the IFC, CMS calculates the reimbursement price as the minimum GDP-adjusted price of the reference countries, as opposed to the average used in the ANPRM. In the ANPRM, the process for calculating the reimbursement price is based on a multi-step procedure: [165]

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162 ANPRM, at 54559.

163 CMS-5528-IFC, at 30-31.

164 ANPRM, at 54559-60.

165 ANPRM, at 54556.

74.1. Calculate an "average international price for each Part B drug included in the model."

74.2. Calculate the International Pricing Index ("IPI"), which is the ratio of total spending under ASP prices to total spending under the average international price, holding volume and mix of drugs constant.

74.3. Calculate a revised IPI to account for the goal of achieving an approximately 30 percent reduction in Medicare spending for included Part B drugs over time.

74.4. For each drug included in the model, multiply the revised IPI by the average international price to calculate the Target Price. If the ASP is less than the Target Price, then ASP is used instead of the Target Price.

74.5. Phase the Target Price in over the 5-year demonstration period using a "blend of ASP and the Target Price." In year 1, the reimbursement price would be 80/20 (80% ASP, 20% Target Price), in year 2 it would be 60/40, in year 3 it would be 40/60, in year 4 it would be 20/80, and in year 5 it would be 100% of the Target Price.

75. In the IFC, instead of calculating an average price based on an international pricing index, CMS will instead calculate the reimbursement price as the minimum GDP-adjusted price of the reference countries. In the IFC, the process for calculating the MFN price is based on a different multi-step procedure:[166]

75.1. Identify available international drug pricing information using CMS's hierarchy of data sources and remove incomplete and low sales volume data, as applicable.

75.2. Adjust volume data so it is in comparable units to that of the HCPCS code and use this adjusted volume to calculate the country-level price.

75.3. Calculate a GDP adjuster for each country, which is calculated as the ratio of a country's GDP per capita to the U.S. GDP per capita. If a country has a GDP per capita higher than the U.S., the GDP adjuster is capped at 1.

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[166] CMS-5528-IFC, at 71-72, 84.

75.4. Divide the country-level price by the GDP adjuster to get the GDP-adjusted country-level price.

75.5. Select the lowest GDP-adjusted country level price, which will be the MFN price (unless the ASP is lower than the MFN price, in which case the ASP will be used instead.)

75.6. Similar to the Target Price in the ANPRM, the MFN price will be phased in over the demonstration period (with certain exceptions). However, the MFN price will be phased in faster than in the ANPRM, increasing by 25 percent per year as compared to 20 percent per year, reaching 100 percent of the MFN price by year 4 of the demonstration.

76. The MFN price outlined in the IFC has the potential to decrease the reimbursement price by substantially more than the IPI price presented in the ANPRM, because the MFN price is based on the minimum of the prices in reference countries, whereas the IPI price was based on the average of the prices in reference countries.

77. By way of example, according to a supporting report for the IFC by the U.S. Department of Health and Human Services, the Medicare Part B price for Cimzia (Certolizumab Pegol, a drug to treat conditions like Crohn's disease and rheumatoid arthritis) in 2018 was 2.21 times as high as the GDP-adjusted *average* price of non-U.S. OECD countries with 60 percent or more of U.S. GDP per capita.[167] In contrast, according to the IFC, the U.S. Average Sales Price for Cimzia was approximately 4 times as expensive as the GDP-adjusted *minimum* price (paid in Australia) among countries included in the MFN model.[168]

78. The large difference between the average prices (proposed in the ANPRM) and the minimum prices (in the IFC) holds more broadly. The Medicare Part B price for the top 50 drugs in 2018 was, on average, 1.52 times as high as the GDP-adjusted *average* price of

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167 Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, "Medicare FFS Part B and International Drug Prices: A Comparison of the Top 50 Drugs," 2020 ("2020 HHS MFN Report"), Table 3.

168 CMS-5528-IFC, Table 6.

countries included in the MFN model.[169] In contrast, according to the IFC, the "illustrative" U.S. ASP for the drugs included in year 1 of the MFN model was, on average, 9 times as expensive as the "illustrative" GDP-adjusted *minimum* price among countries included in the MFN model.[170] By decreasing the reimbursement price, the harms I describe in Section V have the potential to be greater with the MFN model than with the IPI model.

79. Furthermore, because the MFN price is determined by the GDP per capita-adjusted price in the lowest-price reference country, the MFN price will not only not be representative of U.S. valuations for the drug, but it will also not be representative of valuations for the drug in the reference countries. Problems with measuring international drug prices—a problem the IFC discusses at length[171]—will be exacerbated by determining the U.S. price based on the lowest-price reference country, because any country for which measurement of prices is inaccurate will be more likely to be an outlier and therefore more likely to be the minimum.

2. The IFC expands the number of reference countries over the ANPRM.

80. In the ANPRM, CMS was considering a list of 14 countries to include in the IPI: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, and the United Kingdom. CMS' rationale for using these countries is that "they are either economies comparable to the United States or they are included in Germany's market basket for reference pricing for their drug prices, and existing data sources contain pricing information for these countries."[172]

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169 2020 HHS MFN Report, at 15.

170 CMS-5528-IFC, Table 6.

171 CMS-5528-IFC, Section III.E.1.

172 ANPRM, at 54557.

81. The IFC substantially expands the set of reference countries to be included in the basket, deciding to instead base the decision on whether a country should be considered for MFN pricing on "membership in the OECD and GDP per capita relative to the U.S."[173]

82. In addition to the countries listed in the ANPRM, all of which are in the OECD, there are 20 additional OECD countries.[174] According to the IFC, CMS intends to include any OECD country "with a GDP per capita of at least 60 percent of the U.S. GDP per capita."[175]

83. Based on this definition, 22 OECD countries will be used to calculate the MFN during the first performance year of the model: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, and the United Kingdom.[176]

84. The decision to base price on the minimum price among reference countries in the IFC, rather than the average price among reference countries as in the ANPRM, and the decision to expand the list of reference countries combine to make it more likely that the IFC price is a based on a low outlier price. The minimum price of a larger number of countries is more likely to be lower than the minimum price of a smaller number of countries.

85. Five out of the twelve countries that will be the basis for the MFN price during the first performance year, according to the IFC, are countries that were not included in the ANPRM. These five countries (Australia, Luxembourg, Norway, Republic of Korea, and Switzerland) account for almost 55 percent of the "illustrative" quarterly MFN prices in the first performance year.[177]

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173 CMS-5528-IFC, at 67.

174 CMS-5528-IFC, at 67.

175 CMS-5528-IFC, at 67.

176 CMS-5528-IFC, at 68.

177 CMS-5528-IFC, Table 6 and at 67.

86. As a result of how the MFN price is calculated, the lowest price is likely to not only not be reflective of U.S. valuations for the drug, it will also not be reflective of valuations for the drug in reference countries more broadly, nor the countries included in the 2018 ANPRM.

C. The MFN model described in the IFC includes an annually increasing number of drugs

1. The MFN model includes the top 50 drugs by allowable charges and is recalculated annually to identify additional drugs

87. In the 2018 ANPRM, CMS was relatively vague about which drugs it would include in the model. CMS indicated that they would focus on "single source drugs and biologicals (including biosimilars) [including] HCPS codes that contain only products with a single manufacturer, even if they are a multiple source drug."[178]

88. In the 2018 ANPRM, CMS also indicated that they were considering "including more drugs over time, […] prioritizing single source drugs and biologicals […] [and] HCPCS codes for drugs and biologicals that are clinically comparable, but not interchangeable, […] particularly […] [those] used incident to a physician's services."[179] With their incremental addition of new drugs, CMS sought to include "HCPCS codes that encompass at least 75% of allowed charges in Part B."[180]

89. In the 2020 IFC, CMS altered the list of drugs that were to be included, so that "approximately 50 Medicare Part B drugs [would be] in the MFN model for each performance year."[181] To accomplish this, CMS "identified the top 50 drugs by HCPCS code with the highest aggregate 2019 Medicare Part B total allowed charges."[182] The list of drugs included in the MFN model will be updated annually at the beginning of each performance year "using the most recent full calendar year's Medicare Part B claims from

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178 ANPRM, at 54554..

179 ANPRM, at 54554.

180 ANPRM, at 54555.

181 CMS-5528-IFC, at 33.

182 CMS-5528-IFC, at 48.

all providers and suppliers."[183] CMS will then add to the MFN drug list any "drugs (as identified by HCPS codes) that have total allowed charges that fall into the top 50 drugs by spending for that calendar year that are not already on the MFN model Drug HCPCS Codes List."[184]

90. This process will only add HCPCS codes to the list, and any codes that fall out of the top 50 will not be removed from the list. CMS explains that this process of adding, but not dropping, drugs from the list will address the potential for MFN participants to "shift utilization to avoid using drugs subject to the MFN model payment."[185]

2. The MFN model may result in a mix of drugs that expands each year

91. CMS claims that, based on previous spending patterns for high-cost Medicare Part B drugs, the list of drugs included in the model will remain relatively stable.[186] However, this is inconsistent with the fact that they describe the annual update process as a mechanism for adding drugs to the model that were not previously included but experienced an increase in utilization due to MFN participants shifting away from drugs in the model and to drugs not included in the model.

92. Additionally, according to estimates from the CMS Office of the Actuary, "a portion of the savings [(up to 19%)] is attributable to beneficiaries not accessing their drugs through the Medicare benefit."[187] These claims imply that CMS expects the distribution of spending across different drugs to shift at least somewhat, if not considerably, and therefore makes it unlikely that the list of drugs will remain relatively stable over time.

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183 CMS-5528-IFC, at 45.

184 CMS-5528-IFC, at 45.

185 CMS-5528-IFC, at 46.

186 CMS-5528-IFC, at 33.

187 CMS-5528-IFC, at 184.

3. Excluded drugs differ between the ANPRM and the IFC

93. The list of excluded drugs differs slightly between the 2018 ANPRM and the 2020 IFC. Specifically, in the 2018 ANPRM, CMS indicated they would consider excluding "drugs that are identified by the FDA to be in short supply."[188] In the 2020 IFC, CMS indicates that instead of excluding drugs on the FDA shortages list, they will instead exclude "intravenous immune globulin products […] because these products are at higher risk of shortage."[189] In the 2020 IFC, CMS also includes an additional list of excluded drugs that were not listed in the 2018 ANPRM. This list includes vaccines, specific oral Part B drugs (oral anticancer chemotherapeutic agents, oral anti-emetic drugs, and oral immunosuppressive drugs), and generic drugs (i.e., "drugs billed with HCPCS codes that describe a drug product that was approved under a new drug application").[190]

D. The IFC does not include a provision for private-sector vendors proposed in the ANPRM

94. The IPI model in the 2018 ANPRM sought to "reduce participating health care providers' burden and financial risk associated with furnishing included drugs by using private-sector vendors to purchase and take title to included drugs."[191] These vendors would "negotiate prices for drugs, take title to drugs, and compete for physician and hospital business."[192]

95. The ANPRM acknowledged that "[s]ince 2009, physicians have faced growing financial risks under the buy and bill approach, as the prices of Part B drugs have increased. Hospitals have varying ability to negotiate discounts, so some hospitals face similar financial challenges for the outpatient drugs they provide."[193]

96. The MFN model does not include a provision for private-sector vendors. Without vendors, providers bear a higher financial burden and risk. One potential consequence of higher risk

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188 ANPRM, at 54555.

189 CMS-5528-IFC, at 40.

190 CMS-5528-IFC, at 228.

191 ANPRM, at 54547.

192 ANPRM, at 54546.

193 ANPRM, at 54549.

for providers is that physicians may decide not to prescribe particular drugs, given that they risk paying more for these drugs than they get reimbursed from Medicare. This results in harm for certain providers, patients, and manufacturers, as I discuss in more detail in Section V.

97. Moreover, absent vendors, it is unclear whether drug manufacturers will be able to offer different prices on sales to physicians for Medicare and non-Medicare patients. Absent the ability to do so, they may choose not to reduce prices to providers for Medicare sales, and as discussed further in Sections V.A and V.B, this would likely lead to losses for physicians and lack of access to some drugs for patients.

IV. THE IMPLEMENTATION OF THE MFN MODEL DESCRIBED IN THE IFC IS NOT A PROPERLY-IMPLEMENTED TEST

98. When the scale of a proposed regulation is large and its consequences are uncertain, it is of particular importance that the demonstration model is a properly-implemented test in which the regulation's consequences can be evaluated, potential harm from the regulation during the testing period is limited, and the regulation can be improved over time before broad adoption.

99. The MFN model described in the IFC is not set to be implemented in this way. Because the regulation will be implemented nationwide and require mandatory participation by all Medicare Part B patients and providers (with limited exceptions), a proper comparison of outcomes in the tested group of providers and patients to an untested control group is not feasible.[194] Thus, it will not be possible to reliably and rigorously evaluate the proposed regulation's consequences.

100. Moreover, the national and mandatory implementation of the MFN model imposes risk of harm to patients and providers during the "testing" period that could be mitigated to some degree with a properly-implemented test that would apply only to a subset of the US population.

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[194] In contrast, the October 2018 ANPRM proposed a test group (that includes randomly selected geographies, accounting for approximately 50 percent of Medicare Part B spending on separately payable Part B drugs) and a control group (that includes the other half of corresponding spending) during the testing period. ANPRM, at 54553

101. The regulation also differs from tests that the CMMI has run in the past, along a number of dimensions; importantly, other regulations have been implemented as tests with limited scope (e.g. pilots), which enhances the ability to evaluate the regulation's consequences and reduces potential risks of harm.

102. The issues above are exacerbated by the fact that the policy is set to be implemented in the middle of a global pandemic, which makes the evaluation of the policy substantially more difficult and increases potential risks of harm of the proposed policy.

A. The national, mandatory, and immediate implementation of the MFN model is unusual and lacks a proper control group to rigorously and reliably evaluate the effects of the policy

103. The characteristics of the proposed regulation differ from other, ongoing or complete CMMI "initiatives to accelerate the development and testing of new payment and service delivery models," which I reviewed.[195] The proposed regulation is unusual in that:

- it is to be implemented nationally;
- it is mandatory for all qualifying patients and providers; and
- it is to be implemented immediately (only six weeks after announcement of the policy).

104. Most other models I reviewed were voluntary. In a voluntary model, the patients or providers who do not participate in the model can—under certain assumptions—be used as a comparison or control group to determine how outcomes would have changed over

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[195] I omitted from my review: (i) initiatives designed to fund innovation-related initiatives and (ii) initiatives for which details were not available. The former included an initiative to fund innovations in the use of artificial intelligence in predicting healthcare utilization and two requests for information from the public to provide ideas for healthcare innovation. It also included a number of "State Innovation Model" grants, which exclude because they were designed to fund innovation by other entities. However, I note that any "State Innovation Model" grants are testable—under certain assumptions—by comparing against other states for which the innovations are not implemented. I also omitted from my review three initiatives listed by CMMI but for which they did not provide any details. Centers for Medicare & Medicaid Services, "Innovation Models", viewed December 11th, 2020 (https://innovation.cms.gov/innovation-models#views=models&cat=initiatives%20to%20accelerate%20the%20development%20and%20testing%20of%20new%20payment%20and%20service%20delivery%20models&stg=ongoing,ongong).

time but-for the regulation. Among the models that were mandatory, none were implemented on a national scale. In a model that is not implemented on a national scale, geographies or similar types of facilities that were not included in the model can—under certain assumptions—be used as a comparison group to determine how outcomes would have changed over time but-for the regulation. However, in a model that is *both* national and mandatory, there is no comparison group that can be used to determine how outcomes would have changed over time but-for the regulation. The CMS acknowledges in the IFC that because of choices made by the agency, there is, in fact, no "independent comparison group."[196] This was not true in the ANPRM.[197]

105. Acknowledging the lack of a comparison group, the IFC proposes using an interrupted time series methodology without any independent comparison group to evaluate the effect of the regulation.[198] None of the other models I reviewed use an interrupted time series without a control group as an evaluation method, and interrupted time series are typically not the method of choice to evaluate these models. A "difference-in-difference" approach using data on the treated group and control group before and after the policy would be superior and is commonly used to evaluate demonstration models. As is well-established in the empirical economics literature, this type of approach allows to control for systematic differences in outcomes, such as drug utilization and patient well-being, between before versus after the regulation that are unrelated to the policy intervention of interest.[199]

106. An interrupted time series methodology without any independent comparison group can only reliably and accurately estimate the effects of a regulation under very specific circumstances that do not hold in the case of this regulation.

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196 CMS-5528-IFC, at 167.

197 The October 2018 ANPRM proposed a test group (that includes randomly selected geographies, accounting for approximately 50 percent of Medicare Part B spending on separately payable Part B drugs) and a control group (that includes the other half of corresponding spending) during the testing period.

198 CMS-5528-IFC, at 167.

199 See, e.g., Wooldridge, Jeffrey M. Introductory Econometrics: A Modern Approach. 5th edition (2012). Angrist J.D. & Pischke, J-S., Mostly Harmless Econometrics: An Empiricist's Companion (2008).

107. An interrupted time series without any independent comparison group estimates the effects of a regulation by comparing actual outcomes after a regulation to predicted outcomes based on the trend of outcomes prior to the regulation. In other words, *this approach assumes that the trend in outcomes prior to the regulation would have continued in some form but-for the regulation*.

108. The assumption that the trend in outcomes prior to the regulation would have continued but-for the regulation is a strong one, even under normal circumstances, because a myriad of factors can affect the trend in outcomes such as drug utilization, patient well-being, and physician profitability. As I will explain in the following subsection, this is particularly true in a pandemic that has changed the use of a variety of medical treatments.[200] Moreover, as COVID-19 vaccines roll out, people will adjust their medical care, which will again change utilization patterns and render the evaluation methodology less reliable.

109. The IFC is also unusual in the short time between the announcement date and the implementation date (six weeks), compared to other models I reviewed. In the case of the IFC, the short time between the announcement date and the implementation date increases the potential harm from the regulation, because biopharmaceutical companies and providers do not have adequate time to prepare for the regulations.

B. Implementing the MFN model nationally, mandatorily, and immediately in the midst of the COVID-19 pandemic is inappropriate for the purposes of conducting a rigorous and reliable evaluation of the model

110. The IFC does not propose to implement the regulation during regular circumstances; it proposes to implement the regulation during a global pandemic that is likely to independently affect healthcare utilization and outcomes. As a result, the assumptions needed to draw valid conclusions about the effects of the regulation from an interrupted time series, as suggested in the IFC, will likely not hold. The IFC acknowledges that the proposed evaluation approach is unable to adjust for the effects of the COVID-19

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[200] Mehrotra et al., "The Impact of the COVID-19 Pandemic on Outpatient Visits: A Rebound Emerges," The Commonwealth Fund, May 19, 2020, viewed December 9, 2020 (https://www.commonwealthfund.org/publications/2020/apr/impact-covid-19-outpatient-visits).

pandemic. For example, the IFC states that its "impact analysis does not include the effects of the COVID-19 pandemic. Many assumptions such as utilization, mortality, and morbidity are more uncertain than usual due to the pandemic. The direction and magnitude of the financial impact of the pandemic on Part B drug spending is uncertain."[201] This statement in the IFC is inconsistent with the premise that an interrupted time series could be used to reliably evaluate the regulation's effect. If CMS is unable to reliably evaluate the effects of the global pandemic on outcomes now, CMS would be even less able to separate the effects of the global pandemic from the effects of the regulation if the regulation were implemented on January 1, 2021.

V. THE IFC WOULD HARM VARIOUS ACTORS IN THE BIOTECHNOLOGY AND PHARMACEUTICAL VALUE CHAIN

111. The proposed regulation represents a sudden and economically meaningful change to reimbursement for most physician administered drugs prescribed to Medicare patients. In a supporting report for the rule, the Department of Health and Human Services argues that the particular manner in which these types of drugs are currently acquired and reimbursed could make them appropriate for this type of non-market regulation of prices.[202] In particular, the authors express concerns about the fact that medical providers have limited ability and incentive to negotiate price concessions for these drugs with drug manufacturers, because they are reimbursed for these drugs by Medicare based on market prices.[203] That said, the very complexities of this procurement process requires that reimbursement regulations receive careful consideration of the unintended harms that may result from large and sudden changes.

112. My preliminary analysis to date of the proposed regulations leads me to believe that the rapid implementation of this regulation on January 1, 2021 will create distinct harms to patients, providers, and manufacturers. Some of these harms will emerge immediately and are directly a consequence of the speed with which this regulation is implemented. Some

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201 CMS-5528-IFC, at 179.

202 Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, "Medicare Part B Drugs: Trends in Spending and Utilization, 2006-2017," 2020 ("2020 HHS Trend Report"), at 19.

203 2020 HHS Trend Report, at 19.

of these immediate harms will be irreparable and persist long after this litigation. Others will manifest over time and are likely unintended consequences of the regulation that would have been addressed during a more carefully considered policymaking process.

A. The IFC would harm medical providers

113. As described in Section II.C, unlike retail pharmaceutical products, the physician administered drugs covered by the Medicare Part B program are first purchased by medical providers either from a wholesaler or a purchasing organization. These providers are then reimbursed by the Medicare program when they prescribe and administer the drug. The current reimbursement is a function of the average market price of the drug. Under the new system, providers would earn both a flat fee for administering the drug and a payment for the actual pharmaceutical product that is not directly tied to the average purchase price of the drug. This introduces meaningful new concerns for physicians who will now bear risk on the cost of administering the drug, which might cause them to refuse to stock and prescribe certain drugs, based on financial rather than medical considerations. These decisions will be influenced by two factors:

- Many physicians have either already bought existing inventories of these products and/or have entered into long term purchase arrangements with pre-specified prices; and/or
- Even as physicians are able to renegotiate these contracts, many might lack either the bargaining skills or negotiating leverage to obtain prices that make it financially viable to provide all drugs that they currently provide.[204]

114. Both of these potential channels of harm result from the fact that the regulation, as written, does not directly constrain the prices manufacturers charge for their drugs. Instead, it limits the amount that Medicare will reimburse providers for drugs that they have already purchased. As stated in the regulation, medical providers are automatically mandated to be

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[204] Grennan, M., "Bargaining Ability and Competitive Advantage: Empirical Evidence from Medical Devices," Management Science, 2014.

part of the MFN program, regardless of the prices that they pay to the manufacturer: "There will be no specific enrollment activities for MFN participants; rather, their participation will be effectuated by the submission of a claim for an MFN model drug furnished to an MFN beneficiary, and we will apply the MFN model payment to such a claim."[205]

115. In other biopharmaceutical markets, this distinction may not have much economic relevance. However, in the existing "buy and bill" model for physician administered pharmaceuticals, this regulatory approach could meaningfully change economic outcomes for providers. Either because of long term contracts or a lack of negotiating power/ability – providers may find themselves in situations where prescribing and administering these products produces a small or even negative financial return. Furthermore, drug manufacturers may not be willing to immediately lower prices for providers, particularly for providers that treat mostly non-Medicare patients.[206] Faced with the prospect of small or negative returns when treating Medicare patients, providers may avoid relatively unprofitable treatments for Medicare patients or prioritize treating non-Medicare patients, at least until the industry can adapt to and effectuate a sustainable system that responds to a sudden decrease in Medicare Part B reimbursements.

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205 CMS-5528-IFC, at 26. Included are "Medicare participating providers and suppliers that submit a claim for a separately payable drug that is an MFN Model drug furnished to an MFN beneficiary, unless otherwise excluded […] we exclude from the MFN Model the following providers and suppliers: Children's hospitals (defined under section 1886(d)(1)(B)(iii) of the Act); PPS-exempt cancer hospitals (defined under section 1886(d)(1)(B)(v) of the Act); critical access hospitals (CAHs) (defined under section 1820 of the Act); Indian Health Service (IHS) facilities (described in section 1880 of the Act), except when MFN Model drugs are furnished and such service is described in section 1880(e)(2)(B) of the Act; Rural Health Clinics (RHCs) (defined under section 1861(aa)(2) of the Act); Federally Qualified Health Centers (FQHCs) (defined under section 1861(aa)(4) of the Act); hospitals that are not subsection (d) hospitals (as defined in section 1886(d)(1)(B) of the Act) and are paid on the basis of reasonable costs subject to a ceiling under section 1886(b) of the Act; and extended neoplastic disease care hospitals (defined in section 1886(d)(1)(B)(vi) of the Act). In addition, for the first quarter and second quarter of performance year one, we will exclude acute care hospitals that participate in a CMS Innovation Center model under which they are paid for outpatient hospital services furnished to Medicare FFS beneficiaries, including MFN Model drugs, on a fully capitated or global budget basis in accordance with a waiver under such model of section 1833(t) of the Act," CMS-5528-IFC, at 18-19.

206 Drug manufacturers and providers may also face an asymmetric information problem, at least in the near future, in which the provider cannot credibly report, or the manufacturer cannot reliably verify, the number of Medicare Part B patients the provider treated with a certain drug versus the number of non-Part B patients the provider treated with the same drug.

116. Beyond the potential harm to patients from such prescribing decisions described below, the payments for administering drugs to these patients are currently a meaningful portion of revenues for many physician offices. According to MedPAC, for a majority of the highest price drugs covered under the Part B program, at least 75 percent of the purchased volume was acquired for a price that was at or below 102 percent of ASP. These providers were then reimbursed either 104.3 percent or 106 percent of ASP (depending on the time period).[207] For providers acquiring a Part B drug below the existing reimbursement, a sudden implementation of the MFN model, in which the add-on payment for administering drugs would switch to a "single per-dose add-on payment amount of $146.55 (prior to the application of the inflationary factor that applies during the model),"[208] would create economic harms.[209] Even if we assume that prices adjust over time, under the MFN model, many of these providers would receive less revenue from the prescribing and administration of Part B drugs. The magnitude of this harm is a function of both the change in prices resulting from the MFN, as well as whether the drug was above or below average in price prior to the regulation. Without sufficient additional payments for providing other medical services or meaningful cost savings generated in other areas, it may be hard for some of these practices to remain financially viable – which would constitute a harm both for those providers and their patients. For example, recent evidence suggests that losing access to a medical provider can have meaningful costs for patients.[210]

117. The IFC acknowledges that the new policy will "initially decrease add-on payments for MFN model drugs with relatively higher historical applicable ASP-based payment amounts

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207 MedPAC, "Payment policy for prescription drugs under Medicare Part B and Part D," April 30, 2019, at 6.

208 CMS-5528-IFC, at 115. The IFC notes that after applying the inflationary factor, "[t]he resulting per-dose alternative add-on payment amount for the first calendar quarter of performance year 1 (January 1, 2021 through March 31, 2021) is $148.73." CMS-5528-IFC, at 113.

209 The IFC defines a "dose" for the purposes of the MFN add-on payment as "the number of HCPCS billing units reported on a claim line (also called service line or line item)." CMS-5528-IFC, at 109.

210 Sabety, Adrienne H. et al., "Changes in Health Care Use and Outcomes After Turnover in Primary Care", JAMA Internal Medicine, 2020.

per dose."[211] According to the IFC, the "[a]verage 2019 historical add-on payment amounts per dose for the MFN model drugs for performance year one ranged from $10.44 to $2,575.47 per average dose for a drug."[212] Therefore, a sudden change in add-payments to $148.73 per dose in January 2021 can potentially reduce provider revenues by hundreds and even thousands of dollars per dose for certain drugs. For example, for a drug with an average reimbursement of $2,575.47 per dose in the IFC's calculation above, the add-on reimbursement to providers could decrease by more than 90 percent, from more than $2,000 per dose to less than $150 per dose in January 2021.

118. In fact, an analysis conducted by the CMS found that nine out of 35 specialties will experience a decrease in add-on revenues. Those specialties are: "hematology/oncology, medical oncology, neurology, hematology, gastroenterology, gynecological/oncology, infectious disease, hematopoietic cell transplantation & cellular therapy, and dermatology."[213] The IFC also identified hematology/oncology as one of the top three billing specialties for 38 out of the 50 drugs included in year one of the MFN model.[214] Accordingly, implementing the new add-on reimbursements may affect the provision and access to drugs treating some of the most serious diseases such as blood disorders and cancer. At the same time, the new add-on reimbursements can result in a windfall to providers that prescribe drugs with low prices per dose.[215] For example, for a drug with an average reimbursement of $10.44 per dose in the IFC's calculation above, the add-on

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211 CMS-5528-IFC, at 114.

212 CMS-5528-IFC, at 114.

213 CMS-5528-IFC, at 119.

214 CMS-5528-IFC, Table 2.

215 It is also possible that switching from an ad valorem rate (based on prices) to a flat rate (based on dosage) can create different prescribing incentives. In this regard, the IFC has noted that provider behavior regarding frequency of treatment and doses will be monitored in order to discourage MFN providers to maximize the add-on payments. ("We intend to monitor MFN participants through any of the previously described monitoring activities (such as documentation requests, audits of claims data, audits of medical records, etc.) to ensure that MFN Model drugs are not being inappropriately billed (for example, excessive doses or units). We anticipate that this monitoring activity will discourage MFN participants from furnishing smaller and more frequent doses of MFN Model drugs to beneficiaries in order to maximize the alternative add-on payments.") CMS-5528-IFC, at 139.

reimbursement could increase by roughly 15 times per dose, from roughly $10 per dose to roughly $150 per dose in January 2021.

119. Furthermore, the sudden implementation of lower reimbursements and switching to a flat fee per dose with only a six week notice will impose undue administrative burdens and costs on medical providers to navigate and adapt to the new regulation. The sudden implementation, without first testing the MFN model, will also cause uncertainties regarding how each actor in the biopharmaceutical value chain will react to the new Medicare reimbursements. These uncertainties will exacerbate the administrative burdens and costs to medical providers, and it is unlikely that all or even most medical providers will be able to internalize and respond optimally to the new regulation in less than six weeks. As described in more detail below, patients will likely be irreparably harmed from reduced access to treatment, while medical providers navigate and adjust their practices to account for the new reimbursements, and the reduction in access to treatment during this period and beyond is irreversible.

B. The IFC would harm patients

120. The financial harms to providers will ultimately affect their prescribing decisions, and as a result, the harm caused by the policy will also be borne by patients. While some may argue that the practice of medicine is unrelated to financial considerations, there is meaningful economic evidence that the amount paid and the incentives created by payments systems impact how physicians practice. Of particular relevance to the potential harms in this area, Jacobsen et al. (2010) and OIG (2012) both find that when payments for oncology medicines were altered, physicians changed their prescribing patterns.[216] For example, Jacobsen et al. (2010) found that the implementation of the ASP + 6 percent reimbursement system meaningfully changed the providers' financial benefits of chemotherapy treatments. This involved primarily two effects: (1) overall, prescribing chemotherapy was

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[216] Jacobson, Mireille et al., "How Medicare's Payment Cuts For Cancer Chemotherapy Drugs Changed Patterns Of Treatment," Health Affairs, 29:7, 2010, at 1391-1399. U.S. Department of Health and Human Services: Office of Inspector General, "Least Costly Alternative Policies: Impact on Prostate Cancer Drugs Covered Under Medicare Part B," 2012.

less financially beneficial; and (2) prescribing higher priced chemotherapy products resulted in more practice revenue than prescribing lower priced products.

121. Oncologists responded in two ways. First, they increased the amount of chemotherapy that they prescribed, which allowed them to increase total practice revenue. They also shifted patients to the higher priced drugs. Of importance to considering potential harm to patients from a price reduction, the shift to prescribing higher priced chemotherapy products decreased mortality. This means that, prior to the payment reform, physicians appear to have responded to financial incentives in a way that decreased the health of their patients. Taken together, this paper provides important evidence that physicians respond to financial incentives and do so even in areas where patients can ultimately be harmed.

122. The possibility of financial incentives affecting provider prescribing behavior was also discussed by MedPAC in analyzing potential reforms to the ASP + 6 percent rule. In discussing the benefits of a two-quarter lag in updating payment rates, they state: "in theory, the two-quarter lag in the ASP + 6 percent payment rates may provide a disincentive for manufacturers to institute large, rapid price increases because they may cause the providers' acquisition costs to exceed the Medicare payment rate and potentially affect providers' willingness to purchase the product."[217]

123. As described above, the proposed regulation in the IFC will decrease the financial attractiveness of certain drugs and in some cases could result in providers receiving a negative margin on particular products. This could result in providers stopping administering the drug – which is an outcome acknowledged and modeled by the OACT report. Table 11 of the proposed regulation (copied below) identifies savings of 9 percent in 2021, 14 percent in 2022, and 19 percent in 2023 and thereafter from patients having no access to drugs that they previously would have been able to access. This results not from the medical decision of the provider, but from an assumed inability or unwillingness of manufacturers to sufficiently lower prices for Medicare Part B enrollees. While this is the most extreme form of harm to patients identified by the OACT, it is important to also note that they assume ten percent of spending will shift from current providers to 340B

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[217] MedPAC, "Medicare Part B Drug and Oncology Payment Policy Issues," 2016.

providers (i.e., a group of providers that is not as heavily affected by the proposed regulation). In addition, one percent of spending is assumed to shift from the current provider to a non-MFN provider.

Table 1: Table 11 from IFC

TABLE 11—ASSUMPTIONS REFLECTED IN OACT ESTIMATE

	2021	2022	2023	2024	2025	2026	2027
Non-340B providers							
Behavior							
Continued Availability	80%	75%	70%	70%	70%	70%	70%
Altered Availability							
Move to non-MFN	1%	1%	1%	1%	1%	1%	1%
Move to 340B	10%	10%	10%	10%	10%	10%	10%
No Access	9%	14%	19%	19%	19%	19%	19%
Total	100%	100%	100%	100%	100%	100%	100%
MFN Price impact	−16%	−25%	−25%	−25%	−25%	−25%	−25%
340B providers							
Behavior							
Continued Availability	100%	100%	100%	100%	100%	100%	100%
MFN Price impact	0%	-3%	-3%	-3%	-3%	-3%	-3%

124. In total, the OACT analysis contained in the proposed regulation identifies that, in 2021, 20 percent of spending will move away from current providers and 45 percent of that will actually involve patients no longer gaining access to their drugs.[218] From 2023 onward, the OACT assumes that 30 percent of spending will move away from current providers and 63 percent of that will actually involve patients no longer gaining access to their drugs.[219] This will create harm for patients *and* create harm for the providers that will no longer receive payment for prescribing those drugs – an economic activity that was previously profitable. Furthermore, the harm to patients will be immediate and irreparable, because the lack of access to certain drugs, or switching to an inferior treatment, cannot be reversed later. Once

[218] Calculated as 1% + 10% + 9% = 20% and 9% / 20% = 45.0%. See Table 1.

[219] Calculated as 1% + 10% + 19% = 30% and 19% / 30% = 63.3%. See Table 1.

a patient forgoes, delays, or changes treatment, they cannot go back in time to change that decision.

125. The IFC itself also recognizes the likelihood that the MFN pricing rule could cause immediate loss of access to drugs in stating that the exemption for COVID-19 treatments "will minimize any potential for the MFN model to impact rapid, widespread availability of such drugs in the U.S."[220] It explains further that, "[s]ince there may likely be urgent, high demand for such drugs and available supply may be targeted to certain populations, this exclusion allows maximum flexibility for potential changes in drug distribution for such drugs,"[221] recognizing that Americans may fail to obtain sufficient access to such drugs unless they pay more than other countries for them. However, the same "flexibility" obtained by paying higher prices could likewise be important for ensuring continued access for any number of drugs in addition to COVID-19 treatments.

126. The potential lack of access to existing products represents only part of the harm to patients that would result from this regulation. The regulation would immediately disrupt the funding and operations of biotech companies, particularly small biotech startups that rely on venture capital to fund their research. Investing in biotech R&D is both risky and costly. For example, it is estimated that only 12 percent of biologics that enter Phase I clinical trials will eventually come to market.[222] Earlier investments in products that are pre-clinical are even riskier. Individuals invest in these early stage firms knowing that a majority of their investments will fail but that they can earn a sufficiently large return on successes to make up for the failures.

127. As described above, the cost of bringing a drug to market has been estimated to range from under $1 to almost $3 billion. That said, many of the firms making early stage investments are aware that their investments have option value, i.e., even after making their initial risk

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220 CMS-5528-IFC, at 40.

221 CMS-5528-IFC, at 32.

222 "Clinical Development Success Rate 2006-2015," Biotechnology Innovation Organization, June 2016, pp. 7, 20.

investment, they are not compelled to make subsequent investments in products that do not generate sufficiently positive results. Such an option value investing strategy is more valuable when there is more variance in potential returns, i.e., when positive information can result in exceptionally large returns, and negative information can allow firms to cut off projects before making large expenditures.[223] As a result, policies which reduce the potential upside of a product (even if the expected value remains the same) greatly reduce the attractiveness of making a large number of early stage bets. Obviously, those that do so *and* reduce the expected value can cause even greater reduction in these investments.

128. The relationship between the increased innovation caused by potential profits and the reduced access resulting from high prices is often discussed as a tradeoff of static and dynamic efficiency. In the short run, quantity is below the efficient level because of the high price-cost margin. However, these margins provide the incentives for the development of new products. As long as the welfare generated by these new products outweighs the welfare lost by the reduced access in the current period, these policies generate economic value.

129. The proposed policy will cause manufacturers to be less willing to make the large investments necessary to develop physician administered products for conditions that disproportionately affect elderly Americans. This has been demonstrated by a range of economic studies which use different methods to identify the consistent relationship between the potential market size (i.e., profits) and investments in R&D.[224] Of particular relevance to the likelihood of the proposed regulation causing harms to patients, Blume-

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223 Avinash K. Dixit and Robert S. Pindyck, "The Options Approach to Capital Investment," Harvard Business Review, May-June 1995.

224 Acemoglu and Linn (2004) measure potential market size using demographic changes in the U.S. Acemoglu, Daron, Joshua Linn, "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry," The Quarterly Journal of Economics 119 (3): 1049-1090, 2004. Finkelstein, Amy, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," The Quarterly Journal of Economics 119 (2): 527-564, 2004. Dubois, Pierre et al., "Market Size and Pharmaceutical Innovation," The RAND Journal of Economics 46 (4): 844-871, 2015. Blume-Kohout et al., "Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development," Journal of Public Economics 97: 327-336, 2013. Dranove D, Garthwaite C, Hermosilla MI, "Expected Profits and the Scientific Novelty of Innovation," National Bureau of Economic Research, 2020 May 1.

Kohout and Sood (2013) examine the effect of the creation of Medicare Part D (i.e., the government subsidized insurance program for retail pharmaceuticals) on manufacturer investments in clinical trials. These researchers found that the expansion in insurance created by Medicare Part D led to increased investments in trials for products targeting conditions that have a greater share of patients that are over 65.[225] This demonstrates the consistent economic evidence finding the connection between market size and investments in innovation, and that the connection applies directly to the Medicare program.

130. Another closely related piece of evidence supports the contention that the regulation would reduce the number of new drugs. In December, 2019 the White House Council of Economic Advisers (CEA) released an analysis of H.R.3, the Lower Drug Costs Now Act of 2019. Both the IFC and H.R.3 share the central feature of setting U.S. drug prices as a function of those in other developed economies. Describing H.R.3, the CEA stated: "Heavy-handed government intervention may reduce drug prices in the short term, but these savings are not worth the long-term cost of American patients losing access to new lifesaving treatments."[226] The MFN model for Medicare Part B drugs would decrease the incentives to develop physician administered products for conditions that are more likely to affect elderly Americans.

131. Given the heavy involvement of the government in establishing intellectual property protection and in paying for biopharmaceuticals through its various social insurance programs, it is clear that government policies are an important part of this decision. That said, policies to date have largely relied on markets to attempt to balance the preferences for access and innovation. For example, when creating Medicare Part D, the government chose to rely on private firms to administer the program and negotiate formularies, rather than establishing a government price schedule.

132. Under Medicare Part B, reimbursements are determined as a function of the non-government price and therefore reflect the preferences of privately insured U.S. patients.

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225 Blume-Kohout, Margaret E., and Neeraj Sood, "Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development," Journal of Public Economics 97: 327-336, 2013.

226 White House Council of Economic Advisors, "House Drug Pricing Bill Could Keep 100 Lifesaving Drugs from American Patients," December 3, 2019.

In contrast, the proposed reference-pricing system will impose the preferences of governments and patients in those countries on U.S. patients. However, U.S. patients (i) have different preferences for medical spending and end-of-life care than patients in other countries, and (ii) benefit from having access to a wider variety of drugs (due to the size and diversity of the U.S. population).[227] Therefore, the government-imposed, non-market-based MFN prices that the IFC seeks to impose in the U.S. would not reflect the preferences of the U.S. population.

133. While higher prices in the U.S. compared to other countries is often cited as evidence of a market failure, this is not necessarily the case. As a matter of economics, there is nothing wrong with patients that value drugs more paying higher prices than patients that value the same drugs less. Furthermore, by paying higher prices, U.S. patients incentivize the development of drugs that they would like to use. If Medicare paid the same as other countries, then U.S. patients would be made worse off, because a number of drugs that they would be willing to pay high prices for would not be developed.

134. Absent conducting meaningful tests / analyses and sufficient time to study the impacts of the Regulation, it is possible that the price decline overshoots what is optimal in the U.S. (based on a reasonable balancing of innovation versus price mark-ups). At a minimum, looking at the current access to drugs in foreign markets (as is done in the HHS report supporting the regulation[228]) provides an inherently incomplete characterization of potential harms. It may provide some evidence about whether firms will withhold an *existing* product from the market, but it does not provide information about the incentives to develop new products.[229] Importantly, this lack of new products represents its own form of reduced access and harm to patients. Furthermore, the harm to U.S. patients is irreparable, because patients would be permanently deprived of drugs that do not get

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227 Einav, Liran, Amy Finkelstein, and Atul Gupta, "Is American Pet Health Care (Also) Uniquely Inefficient?" American Economic Review, 107 (5): 491-95, 2017.

228 2020 HHS MFN Report.

229 Even though it may provide evidence about how manufacturers might approach an entire market, it does not provide information about whether they would be willing to avoid smaller portions of a market, such as being unwilling to lower prices for physicians that treat a small number of Medicare patients or on products that have a small amount of exposure to Medicare.

developed and patients would be denied timely access to drugs for which their development or approval for a new indication is delayed due to the immediate implementation of the MFN model.

C. The IFC would harm biopharmaceutical manufacturers

135. The sudden implementation of the proposed policy on January 1, 2021 would also be expected to cause an immediate decline in revenues and profits for manufacturers. This unexpected loss in revenues and profits will come from, at least, two channels. First, the non-market-based lowering of prices by the regulation will decrease the revenues and profits on all products sold under the MFN. Second, for some products, prices will not adjust sufficiently for providers to be willing to use the product. While it is true that this would result from a decision of firms to not lower prices, this decision would be in response to the non-market-based reimbursement system created by the regulation and therefore reflects a harm caused by the policy.

136. In considering this harm, it is important to realize that firms have already made substantial sunk investments into the affected products with an expectation of a particular time period of pricing power. Therefore, this (ex post) lowering of prices would reflect an economically meaningful financial loss from some investments that otherwise would not have been made.

137. Beyond products that are on the market, there are a series of products in various stages of development that may no longer be financially viable under a regime of MFN pricing. Even if firms choose to not continue to develop those products, the investments made to date that would have been financially viable (in expectation) are a loss caused by the proposed regulation.

138. The magnitude of the potential loss to manufacturers depends, in part, on ways in which these firms are able to respond to the proposed regulation. At a minimum, there is a question of how manufacturers may change their international prices. Existing economic theory and empirical evidence would suggest that these firms will attempt to increase their

price in the reference priced market.[230] While such higher prices would not be optimal in a world without reference pricing, they would likely become optimal under the regulation, which would effectively force manufacturers to pass along international discounts to the larger U.S. market. However, the amount of lost U.S. revenue manufacturers can recover by attempting to negotiate higher prices in foreign markets depends on how responsive these foreign governments are. In responding, it is unlikely that small countries will consider the potential impacts of their decisions on broader innovation—as these smaller countries will be tempted to free ride off of the investments of their larger counterparts—and the ability of manufacturers to negotiate higher prices may thus be limited.[231]

139. As manufacturers consider their optimal response, an additional category of financial harms will come from these firms finding it optimal to exit certain foreign markets which will not accept higher prices. Again, while this will be a decision of manufacturers, it is a result of them optimizing under the constraints created by the proposed regulations and therefore represents harm.

140. The MFN model would, as described above, reduce investments in biopharma R&D by reducing the maximum and/or expected returns from developing a new treatment. The reduction in returns can decrease the ability of biotech firms, particularly small biotech startups, to secure funding for their business. A policy that reduces funding can be particularly harmful to small biotech startups that rely on outside capital to finance their operations. Furthermore, if unilateral action by a government agency that lowers prices / reimbursements immediately and substantially, without going through the normal rulemaking process, is allowed to go into effect, this would further add to the uncertainties (e.g., Knightian uncertainty) to the prospects of future investments in the biotech industry and chill investment. The harm would be immediate and irreparable to biotech firms that

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230 M. Duggan and F. Scott Morton, "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing," Quarterly Journal of Economics, Feb 2006, 121(1): 1–30; L. Maini and F. Pammolli, "Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market," Working Paper, April 9, 2020.

231 Goldman, Dana and Lakdawalla, Darius, "The Global Burden of Medical Innovation," January 30, 2018, viewed December 11, 2020 (https://www.brookings.edu/research/the-global-burden-of-medical-innovation/).

cannot secure timely funding to start or continue their R&D. Even if the firms can secure funding at a later time, they cannot recover the research time lost, and, in some cases, the R&D may no longer be profitable to pursue due to, for example, pending patent expirations.[232]

141. Similar to the harm caused to medical providers, the sudden implementation of the MFN, with only a six week notice, would also impose undue administrative burdens and costs on manufacturers to navigate and adapt to the new regulation (e.g., adjusting prices and distribution systems). One example of such burdens is the IFC's requirement to "exclude from the calculation of the manufacturer's ASP any units of an MFN model drug."[233] I understand that compliance with this requirement would imply that manufacturers need to track which of their sold drugs ultimately get administered to Medicare Part B patients versus other patients. This information is currently not readily available to most manufacturers, and it is unlikely that they will be able to fully comply with this requirement in just six weeks.

142. The sudden implementation, without first properly testing the MFN model, will also cause uncertainties regarding how each actor in the biopharmaceutical value chain will react to the new Medicare reimbursements. These uncertainties will exacerbate the administrative burdens and costs to manufacturers, and it is unlikely that all, or even most, manufacturers will be able to internalize and respond optimally to the new regulation in only six weeks.

VI. THE ECONOMIC IMPACTS OF THE COVID-19 PANDEMIC DO NOT JUSTIFY IMPLEMENTING THE IFC IMMEDIATELY

143. I understand that CMS is attempting to implement the IFC without following normal rulemaking requirements related to notice and comment periods. In particular, the IFC states that "there is good cause to waive the notice and comment requirements […] because of the particularly acute need for affordable Medicare Part B drugs now, in the midst of the

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232 Budish, Eric et al.. "Do Firms Underinvest in Long-term Research? Evidence from Cancer Clinical Trials," American Economic Review 105.7. 2015, pp. 2044-85.

233 CMS-5528-IFC, at 162.

COVID-19 pandemic."[234] In this section, I explain that this motivation is misguided for a number of reasons.

A. The IFC will immediately reduce some Medicare enrollees' access to their current drugs

144. While CMS claims that the IFC will "prevent stinting on care"[235] that may otherwise occur in response to financial hardship due to the pandemic, the IFC actually threatens to *cause* "stinting on care" because, as I discussed above, patients could suffer immediate loss of access to some drugs. Specifically, providers will likely reduce administering certain drugs to Medicare Part B patients, because the IFC will reduce the financial attractiveness of administering those drugs, potentially even to the point of turning their margins negative. As a result, Medicare patients may be unable to obtain these drugs. Again, this is an outcome acknowledged and modeled by the OACT report, which finds savings of 9 percent in 2021 (and even larger savings in subsequent years) from patients losing access to drugs that they can currently access.[236] Therefore, in emphasizing the importance of patient care during the COVID-19 pandemic, CMS is actually raising a strong argument for why the IFC should *not* be implemented, let alone rushed through contrary to normal rulemaking requirements just as CMS is "currently seeing a new surge in COVID-19 cases."[237]

B. Most Medicare enrollees are not in the labor force and most have supplemental insurance

145. Even setting aside loss of access to drugs caused by the IFC, the proportion of Medicare Part B beneficiaries at risk of "stinting on care" due to financial hardship caused by the pandemic is likely smaller than may be commonly believed. While the IFC claims that "the COVID-19 pandemic has led to historic levels of unemployment in the U.S.,"[238] Medicare

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234 CMS-5528-IFC, at 218.

235 CMS-5528-IFC, at 217.

236 CMS-5528-IFC, at 184.

237 CMS-5528-IFC, at 218.

238 CMS-5528-IFC, at 217.

beneficiaries are primarily 65 years of age or older,[239] and the majority of this age group does not depend on employment income. For instance, the Bureau of Labor Statistics reports that just 19.5 percent of this age group participated in the labor force in November 2020.[240,241] Moreover, as of November 2020, the unemployment rate among Americans, 65 years or older (5.5 percent) is lower than that of other U.S. populations (e.g., 6.7 percent for men, 16 to 64 years old, 6.2 percent for women, 16 to 64 years old, 6.5 percent overall, 16-64 years old), and the change in unemployment rate of Americans 65 years or older over the past year (2.8 percent in November 2019 to 5.5 percent in November 2020) has not been considerably different than that of 16 to 64 year old Americans (3.3 percent in November 2019 to 6.5 percent in November 2020). Similarly, the change in the participation rate, i.e., the share of the population that is in the civilian labor force, over the past year among Americans 65 years or older (20.6 percent in November 2019 to 19.5 percent in November 2020) has not been considerably different than that of 16 to 64 year old Americans (74.3 percent in November 2019 to 72.7 percent in November 2020).

146. In addition, approximately 81 percent of Medicare enrollees had supplemental insurance that covers some portion of their cost sharing in 2016.[242] Given the lower out-of-pocket costs associated with prescription drugs for this group, financial hardship due to the

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239 Kaiser Family Foundation, Distribution of Medicare Beneficiaries by Eligibility Category, viewed December 10, 2020 (https://www.kff.org/medicare/state-indicator/distribution-of-medicare-beneficiaries-by-eligibility-category-2/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D).

240 In November 2019, 20.6 percent of Americans, 65 years of age or older participated in the labor force. U.S. Department of Labor, Bureau of Labor Statistics, "The Employment Situation – November 2020," viewed December 8, 2020 (https://www.bls.gov/news.release/pdf/empsit.pdf).

241 Consistent with this, in the U.S. Census Bureau's 2019 Current Population Survey (CPS), 24 percent of respondents, 65 years or older, report income from wages and salaries and earnings from self-employment. In contrast, 44 percent report retirement income and 31 percent report pension income. U.S. Census Bureau, Current Population Survey, Annual Social and Economic Supplement, viewed December 9, 2020 (https://www.census.gov/data/tables/time-series/demo/income-poverty/cps-pinc/pinc-08.html).

242 These 81 percent included employer-sponsored insurance (30 percent), Medigap (29 percent), and Medicaid (22 percent). Supplemental insurance "typically covers some or all of Medicare Part A and Part B cost-sharing requirements and, in some instances, covers benefits Medicare does not." Kaiser Family Foundation, Sources of Supplemental Coverage Among Medicare Beneficiaries in 2016 (Nov. 28. 2018), viewed December 11, 2020 (https://www.kff.org/medicare/issue-brief/sources-of-supplemental-coverage-among-medicare-beneficiaries-in-2016/).

pandemic is unlikely to prevent individuals in this group from accessing the drugs they need (provided, at least, that the IFC does not prevent them from accessing those drugs itself).

C. The IFC is not a properly-targeted policy instrument to alleviate the financial hardships associated with the COVID-19 pandemic

147. While the burden of cost sharing for Medicare enrollees who lack supplemental insurance is a long-standing economic issue that was discussed in the October 2018 ANPRM,[243] the IFC is a blunt tool with which to attempt to address it. Consider an individual who needs one unit of a given drug and faces a 20 percent coinsurance payment. In the first year of the MFN model, even if the MFN price of the drug is zero (and, again, assuming the drug even remains accessible from the individual's physician), the individual's out-of-pocket expense will decrease by just five percent (i.e., 20 percent of 25 percent, where the price will fall by 25 percent based on the one-quarter weight of the MFN price – in this hypothetical example, zero – in the first year). By contrast, CMS could decrease out-of-pocket costs by 20 percent by not implementing the IFC and instead implementing much more direct relief – namely, waiving cost sharing for the duration of the pandemic, as it has already done, for example, for COVID-19 testing. CMS could also reduce Medicare premiums or deductibles, but belying its purported concern for financial hardships during the pandemic, in November 2020, CMS announced an *increase* in Medicare premiums and deductibles for 2021. [244]

148. In addition, while financial hardship due to the pandemic among vulnerable populations is certainly of great concern, there is another important group that is affected by the pandemic and that stands to be affected by the IFC – the physicians and other health care workers on the front line of the pandemic response. As I discussed above, if the IFC takes effect, the

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243 ANPRM, pp. 54557-54558.

244 CMS, "2021 Medicare Parts A & B Premiums and Deductibles," November 6, 2020, viewed December 11, 2020 (https://www.cms.gov/newsroom/fact-sheets/2021-medicare-parts-b-premiums-and-deductibles#:~:text=Medicare%20Part%20B%20Premiums%2FDeductibles&text=The%20standard%20monthly%20premium%20for,deductible%20of%20%24198%20in%202020).

sudden implementation of lower reimbursements and switching to a flat fee per dose with only a six week notice will impose undue administrative burdens and costs on medical providers. Imposing such costs at exactly the time that CMS is "currently seeing a new surge in COVID-19 cases"[245] would thus place even greater burdens on the medical professionals who are already stretched to the limit providing the urgent care upon which we are all depending. It would also impose undue burdens and costs on drug manufacturers working to develop and launch treatments directed to COVID-19.

VII. CONCLUSIONS

149. My preliminary analysis to date, as described above, leads me to a number of conclusions.

150. First, the economics of the new regulations in the IFC are materially different than those proposed in the October 2018 ANPRM. There are material differences in the geographic scope of the test (select geographic areas versus nationwide), reference price for Medicare Part B reimbursements (average versus minimum international prices), and provider procurement of Medicare Part B drugs (vendor model versus "buy and bill" model).

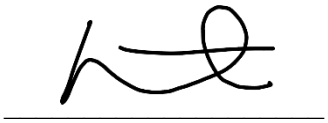
151. Second, the implementation of the MFN model described in the IFC is not a properly-implemented test. The IFC is set to be implemented nationwide and requires mandatory participation by all Medicare Part B patients and providers (with limited exceptions). Therefore, a proper comparison of outcomes in the tested group of providers and patients to an untested control group is not feasible and it will not be possible to reliably and rigorously evaluate the consequences of the MFN model.

152. Third, the IFC would harm various actors in the biotechnology and pharmaceutical value chain. The implementation of the regulations only six weeks after the IFC was issued will create distinct harms to providers, patients, and manufacturers. Some of these harms will emerge immediately and are directly a consequence of the speed with which this regulation is implemented. Some of these immediate harms will be irreparable and persist long after this litigation. Others will manifest over time and some are likely unintended consequences

[245] CMS-5528-IFC, at 218.

of the regulation that would have been addressed during a more carefully considered policymaking process.

153. Fourth, the economic impacts of the COVID-19 pandemic do not justify implementing the IFC immediately. While CMS claims that the IFC will "prevent stinting on care" that may otherwise occur in response to financial hardships due to the pandemic, the IFC actually threatens to cause "stinting on care" by reducing Medicare enrollees' access to drugs. To the extent that CMS aims to alleviate the financial hardships of Medicare enrollees, there are other ways to provide direct economic relief.



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